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*Wetzel, N. C., W. C. Fargo, J. H. Smith and J. Helikson: Growth Failure in School Children as Associated with Vitamin B_{12} Deficiency—Response to Oral Therapy, Science, 110:651, 1949.

**McClure, F. J.: Fluorine in Foods, Public Health Reports, 64:1061, 1949.

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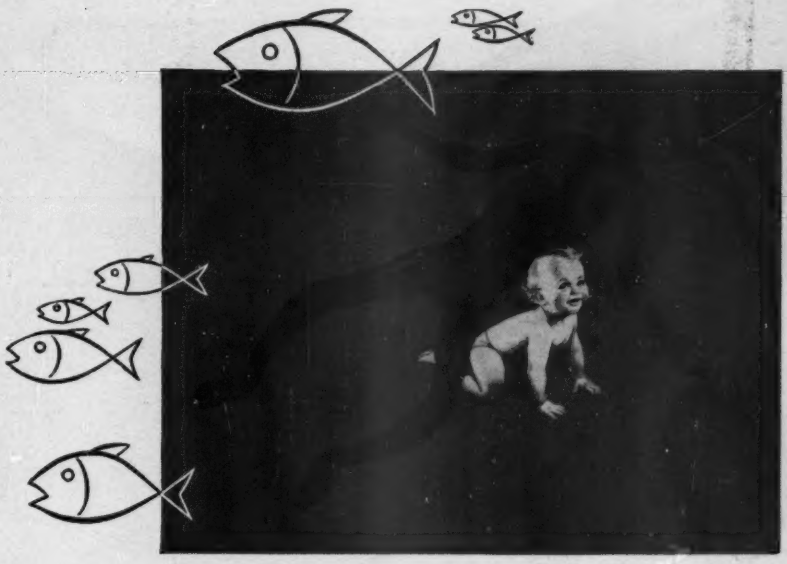

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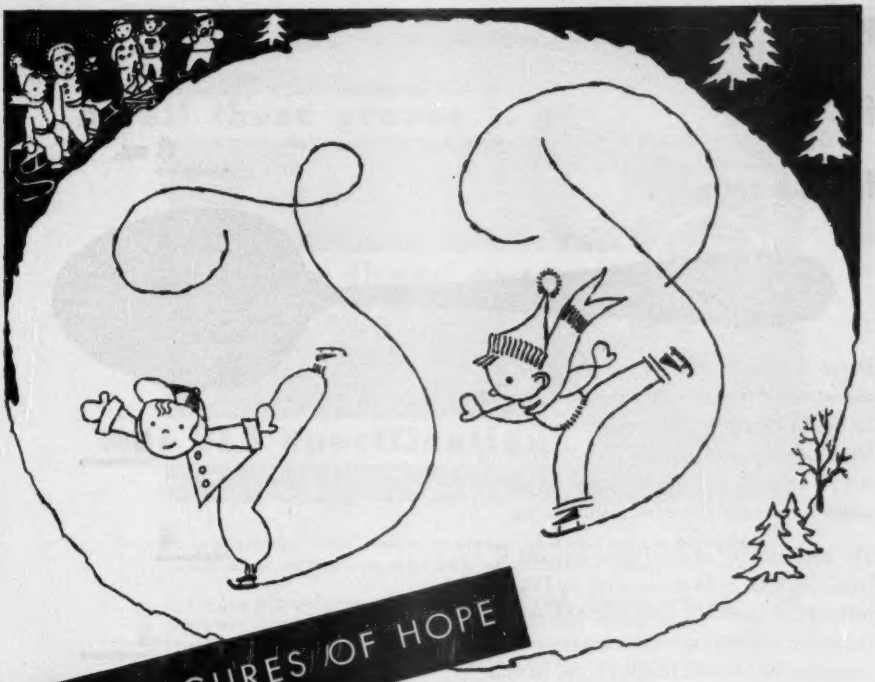

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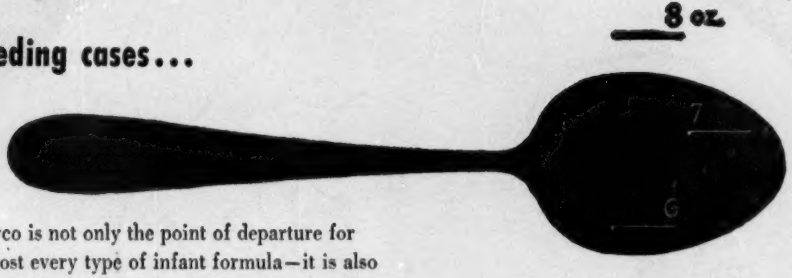

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**Pitt, C.K.: The Art and Science of Artificial Infant Feeding, J.M. Asso. Ala. 19:101 (Oct.) 1949.*

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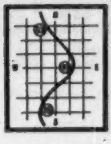

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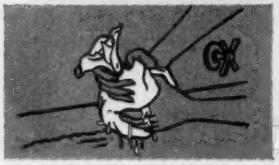

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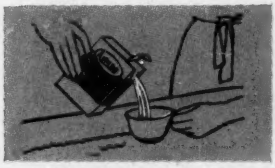

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Most, H., and Van Assendelft, F.:
Ann. New York Acad. Sc. *53*:427 (Sept. 15) 1950.

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Dowling, H. F.; Lepper, M. H.; Caldwell, E. R., and Spies, H. W.: Ann. New York Acad. Sc. *53*:433 (Sept. 15) 1950.

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VOLUME 81 JANUARY 1951 NUMBER 1

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CIRCULATORY DISEASES OF THE KIDNEYS IN INFANCY AND CHILDHOOD

WOLF W. ZUELZER, M.D.
SEYMOUR CHARLES, M.D.
RUBEN KURNETZ, M.D.
WILLIAM A. NEWTON Jr., M.D.
AND
RICHARD FALLON, M.D.
DETROIT

INTRODUCTION

IN INFANTS parenchymal diseases of the kidneys other than those associated with congenital anomalies, pyelonephritis and tumors are regarded as rarities. In this age group glomerulonephritis is uncommon and renal disease of vascular origin is virtually unknown. The experience in our laboratory over the last 10 years indicates, however, that a variety of major injuries to the renal parenchyma, based on vascular disturbances, occur in infants with sufficient frequency to warrant attention.

Between 1940 and 1950 there were 40 cases of major renal disease associated with vascular dysfunction seen among 2,058 autopsies performed on infants and children in this department. This group does not include cases of renal infarct or focal embolic glomerulonephritis secondary to bacterial endocarditis. Of the 40 patients, 34 were infants. In the same 10 year period 18 patients with acute or chronic glomerulonephritis were studied at autopsy, and only two of these were under 2 years of age.

The following is the pathological classification of the 40 cases:

	No. of Cases
Bilateral (symmetrical) cortical necrosis	11
Acute diffuse glomerular thrombosis	2
Necrotizing arteriolitis (malignant hypertension)	2
Arterial occlusion with total infarction of one or both kidneys	5
Generalized ischemic atrophy	1
Thrombosis of renal or intrarenal veins	12
Diffuse hemorrhagic infarction without thrombosis	2
Lower nephron nephrosis	5

The autopsy findings in this group frequently furnished an explanation for symptoms of renal disease that had been puzzling to the clinicians in charge of the patients. Oftener the demonstration post mortem of major diffuse renal disease was altogether an unexpected finding, indicative of the need for closer observation

From the Children's Hospital of Michigan and the Departments of Pediatrics and Pathology, Wayne University College of Medicine.

of such patients. Awareness of the occurrence of these conditions in early life and familiarity with the situations in which they may arise are required if further progress is to be made in the understanding and management of renal disease in infancy and childhood.

I. SYMMETRICAL CORTICAL NECROSIS

WOLF W. ZUELZER, M.D.
RUBEN KURNETZ, M.D.
and
SEYMOUR CHARLES, M.D.

SYMMETRICAL cortical necrosis of the kidneys has been regarded as uncommon at any age. Until recently only about 100 cases have been published.[1] The occurrence of symmetrical cortical necrosis of the kidneys in infants was unknown until 1949, when Campbell and Henderson [2] described two instances, one in a 5 month old infant, the other in a 9 week old infant.

Originally the disturbance was thought to be a specific complication of pregnancy, but it is now clear that it can occur in either sex at any age. According to the comprehensive review by Duff and Murray,[1] the etiology of symmetrical cortical necrosis is varied. Of the cases in which pregnancy was not a factor, the majority seem to have been associated with acute infection, such as diphtheria, scarlet fever, pneumonia or malaria. Poisoning with a variety of substances, shock following trauma, extreme dehydration and purpura have also been described as initiating events. In some instances no etiological factor could be discovered. Experimentally, lesions identical with those of symmetrical cortical necrosis have been produced in rabbits by the injection of Staphylococcus toxin.[3]

The clinical picture as seen in adults is characterized by oliguria and eventual anuria. Before the secretion of urine is suppressed, albuminuria is the rule and red corpuscles, leukocytes and casts are usually present in the urine. Edema is not a constant feature of symmetrical cortical necrosis, and the blood pressure does not show a characteristic trend. The patients remain mentally alert, but terminal convulsions are common. The course of the illness is short, leading to death in four to 12 days. Since the diagnosis is usually made post mortem, it is conceivable that milder cases with reversible lesions may occur.[1]

The pathological picture is that of ischemic necrosis of the renal cortices, varying somewhat in extent and degree, probably depending largely on the duration of the process before death. In the least severe cases the appearance of the lesions resembles that of multiple small infarcts separated by areas of relatively intact tissue. In cases of maximal severity a bandlike zone of necrosis extends through the entire cortex sparing only occasional small streaks and islands

1. Duff, G. L., and Murray, E. G. D.: Bilateral Cortical Necrosis of the Kidneys, Am. J. M. Sc. **201**:428, 1941.

2. Campbell, A. C., and Henderson, J. L.: Symmetrical Cortical Necrosis of the Kidneys in Infancy and Childhood, Arch. Dis. Childhood **24**:269, 1949.

3. (*a*) DeNavasquez, S.: Experimental Symmetrical Necrosis of the Kidneys Produced by Staphylococcus Toxin: Study of Morbid Anatomy and Associated Circulatory and Biochemical Changes, J. Path. & Bact. **46**:47, 1938. (*b*) Trueta, J.; Barclay, A. E.; Franklin, K. T.; Daniel, P. M., and Pritchard, M. M. L.: Studies of the Renal Circulation, Springfield, Ill., Charles C Thomas, Publisher, 1947.

of renal tissue. A variable admixture of hemorrhage contributes to the gross and microscopic picture. Tubules and glomeruli are in varying stages of necrosis or necrobiosis. The blood vessels may show necrosis or fibrinoid degeneration of their walls or thrombosis, but such structural changes are by no means constant. When present, they affect characteristically the interlobular arteries and the afferent vessels.

It is generally agreed that the necrosis is the result of cortical ischemia for which either structural or functional changes in the small renal arteries are responsible.[4] Vasospasm or dilatation and stasis in these vessels are thought to be the initiating events in cases in which morphological lesions cannot be found. The work of Trueta and his associates, who demonstrated a potential arteriovenous shunt within the kidney permitting blood to bypass the cortex and to flow directly through the juxtamedullary glomeruli into the medulla, has provided a widely accepted explanation for the mechanism of cortical ischemia on a functional basis. These authors showed that neurovascular stimuli can invoke the shunt mechanism and deprive the cortical tissues of their blood supply.

The pathological picture of symmetrical cortical necrosis was encountered in 11 cases studied in this laboratory. With one exception, all the patients were young infants whose age ranged from 1 day to 7 months. The precipitating illnesses were varied. Severe diarrhea and dehydration were the initial complaints in five cases. Staphylococcus septicemia was the primary illness in one case. There was one case each of the following conditions: severe postoperative shock; erythroblastosis fetalis; a severe shocklike state following difficult delivery in a newborn infant, and congenital heart disease of the cyanotic type. The eleventh patient was a 12 year old girl with infected trophic ulcers secondary to a meningocele who died with the clinical picture of overwhelming sepsis. All but one of the patients had received sulfadiazine or its sodium derivative in the customary dosage, though in some instances the drug had been given only a few hours before death or after the signs of renal involvement were already evident.

A clinical diagnosis of renal disease was rarely entertained in this group of patients, partly because of the difficulties inherent in the collection of urine specimens of infants and the estimation of the urinary output in this age period. The lack of objective clinical signs pointing to disturbance of the kidneys and the predominance of symptoms seemingly or actually related to the primary illness or to therapeutic measures contributed to the concealment of the renal lesion during life. Some patients may have died of the effects of their initial illness before manifestations of kidney disease had time to develop.

Other writers, notably Dunn and Montgomery [4] and Campbell and Henderson,[2] have commented on the fact that symmetrical cortical necrosis is often an unexpected postmortem finding. The paucity of clinical leads and the diagnostic difficulties are illustrated by the records of our patients. Edema was noted in only one case. In only one instance was there a record of the blood pressure. Oliguria or anuria was present in five cases but usually was not appreciated as a symptom of organic kidney disease. The decrease in the urinary output was either explained on the basis of dehydration or was followed by death so rapidly that its

4. Dunn, J. S., and Montgomery, G. L.: Acute Necrotizing Glomerulonephritis, J. Path. & Bact. **52**:1, 1941. Duff, Lyman and Murray.[1] Campbell and Henderson.[2]

significance was not suspected. Either because of oliguria or as the result of circumstance, a urine specimen was not obtained in five of the 11 cases. Of the other six patients, three had albuminuria and two of these had hematuria as well. In three of four cases in which tests were made the blood urea nitrogen was elevated.

Death occurred within one to 49 days from the onset of the original illness, but information relating to renal function was so scanty in the majority of cases that the duration of the process in the kidneys could not be determined on clinical grounds even in retrospect. From the pathological findings it was evident, however, that the renal lesions had been present for a relatively short time before death. Probably no patient survived for more than a week, and in most cases the duration was estimated to be considerably less.

REPORT OF CASES

Case 1.—G. P., a 5 day old Negro boy, born at term without complications, had seemed healthy until the onset of diarrhea at 4 days of age. At the time of admission there was evidence of weight loss, dehydration, acidosis and lethargy. The carbon dioxide content of the blood was 5.6 milliequivalents per liter. The white blood cell count was 50,000 per cubic millimeter. The hemoglobin concentration of the blood was 18.8 Gm. per 100 cc. Blood cultures remained sterile. The patient voided only once, and this urine specimen could not be collected. Repeated catheterization of the bladder thereafter yielded no urine. The blood urea nitrogen level was 75.8 mg. per 100 cc. The patient received intravenous infusions of isotonic salt solution, 10 per cent dextrose solution, plasma and 5 per cent sulfadiazine sodium in customary doses. He began to vomit dark brown material. The abdomen became distended, cyanosis developed and the body temperature fell to 95 F. The child was in a shocklike state, with cold clammy skin, and died 36 hours after admission.

The autopsy disclosed multiple areas of hemorrhage and early gangrene in the upper part of the small intestine, pulmonary edema and congestion and a purulent exudate in the right middle ear. The kidneys were slightly enlarged and soft. The cortex was brownish red with occasional lighter yellow sunken areas. The cut surface appeared dry and granular, with loss of the usual markings. The cortex was sharply but irregularly demarcated from the medulla by a deep red serpiginous line of hemorrhagic appearance. Cultures of heart blood and material from the lungs, liver and middle ears 23 hours after death all yielded coagulase-positive Staphylococcus pyogenes var. aureus.

Microscopic examination disclosed recent thrombosis (fig. 1) and here and there acute arteritis in the small vessels of the mesentery and small intestine, accounting for the gangrenous and hemorrhagic changes seen grossly.

In sections of the kidneys a nearly uniform picture of necrosis of all cortical elements was seen. A narrow bandlike zone directly beneath the capsule had been spared, and there maximal engorgement of the glomeruli was evident. The remainder of the cortex had undergone necrosis of variable degree (fig. 2). In most areas only blurred shadow-like outlines of glomeruli and tubules could be identified (fig. 3). Here and there, especially in the depth of the cortex, occasional tubules with fading or markedly pyknotic nuclei and deeply acidophilic cytoplasm were found, and in such areas the glomeruli were likewise less severely damaged. In such areas it was evident that the proximal convoluted tubules and loops of Henle were damaged to a severer degree than the distal or the collecting tubules. In most fields, however, necrosis was already complete in all renal elements. By contrast, the medulla appeared intact save for marked venous congestion.

The larger intrarenal arteries were free of visible changes. The intima of the interlobular and afferent arteries had undergone hydropic and fibrinoid swelling (fig. 4). Occasionally early patchy necrosis of the media was also evident. The lumens were markedly dilated and filled with masses of red blood cells that gave the appearance of being agglutinated. Thrombosis was not encountered in the renal vessels as it was in the mesenteric arterioles.

Case 2.—B. D., admitted at the age of 12 hours, was born to an Rh-negative mother at full term after an uneventful pregnancy. He was cyanotic and icteric, liver and spleen were

enlarged, the skin was covered with petechiae and the heart rate was 40 a minute. The hemoglobin concentration of the blood was 10 Gm. per 100 cc., and the nucleated cell count was 115,000 per cubic millimeter. Rh antibodies were demonstrable in the mother's as well as the patient's serum, and the Coombs test on the patient's erythrocytes gave a positive reaction.

The patient appeared moribund but improved temporarily under treatment. He was given oxygen and multiple small blood transfusions and, in addition, received intravenous infusion

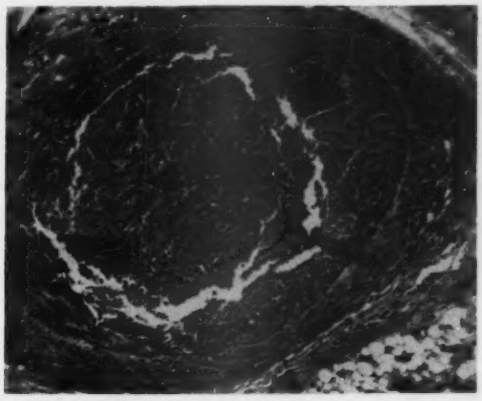

Fig. 1 (case 1).—Recent thrombus in small branch of superior mesenteric artery.

Fig. 2 (case 1).—Low power view of renal cortex. Note irregular dark necrotic cortical zone demarcated from medulla. Lighter appearance of area on the left results from marked interstitial edema.

of 10 per cent dextrose solution and sulfadiazine sodium in 5 per cent solution. Urine specimens obtained during the first three days in the hospital contained bile and occasionally sugar but were otherwise normal. During the last two days the patient did not void. At this time vomiting and marked abdominal distention were noted, and the infant died in shocklike condition at 5 days of age.

The findings at autopsy were compatible with the clinical diagnosis of erythroblastosis. There were icterus, splenomegaly, hepatomegaly, focal pulmonary hemorrhages, terminal

aspiration of stomach contents into the bronchi and congestion of blood vessels in the splanchnic area. The kidneys were soft, yellowish brown, with hemorrhagic striae in the deeper portions of the cortex. Microscopically, extramedullary hemopoiesis was marked in both spleen and liver. In the liver there was also focal necrosis.

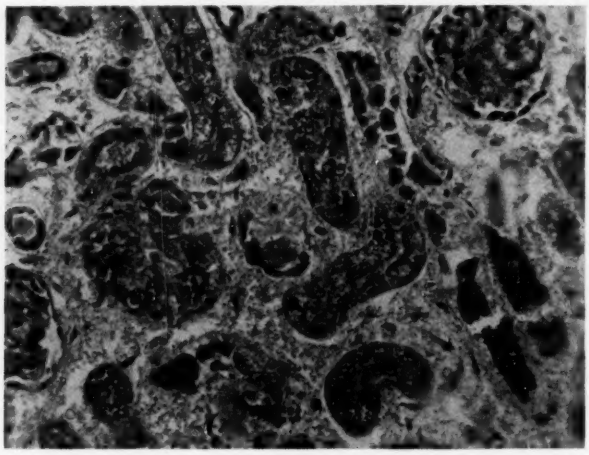

Fig. 3 (case 1).—Representative field of cortex seen with higher magnification. Note necrosis and edema.

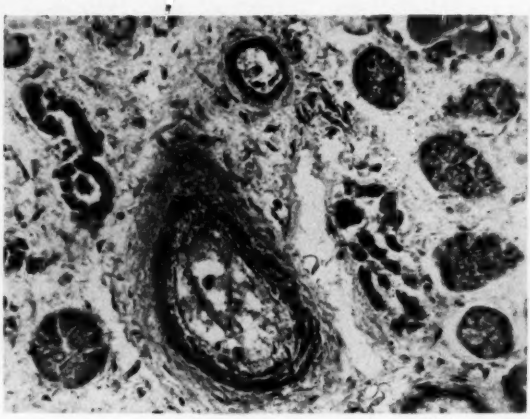

Fig. 4 (case 1).—Cross section of interlobular artery. Note hydropic and fibrinoid swelling and necrosis of intima with marked narrowing of the lumen. Edema and necrosis are evident in adjacent tissue.

The histological appearance of the kidneys was virtually identical with that described in case 1 (fig. 5). A thin border zone at the periphery of the cortex was intact except for maximal engorgement of the glomerular capillaries. The tubules of the remainder of the

cortex were necrotic (fig. 6). In the glomeruli the process of necrosis was usually in its earliest stage but the dilatation of the capillary loops was striking. Throughout the necrotic tissue there were many small streaky hemorrhages distributed at right angles to the surface.

CASE 3.—T. A., a 3 month old boy, cyanotic since birth, had been lethargic for a few days. He had always done poorly and had undergone several attacks of diarrhea and vomiting. At

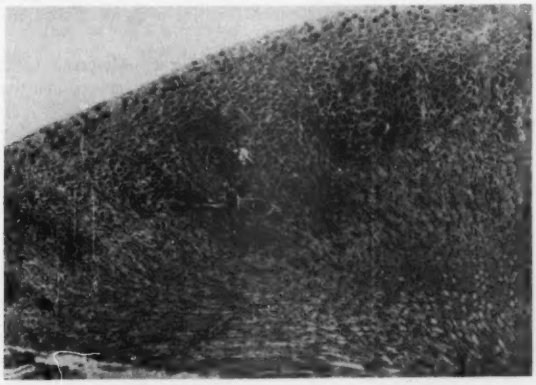

Fig. 5 (case 2).—Low power view of kidney. Note irregular mottling due to confluence of dark necrotic and hemorrhagic areas.

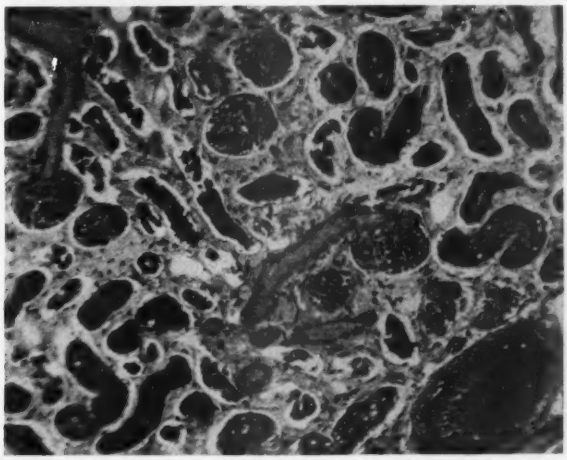

Fig. 6 (case 2).—Typical appearance of cortex. Note edema of tubules, marked dilatation and congestion of afferent arterioles and interlobular artery (upper left corner). Edema and hemorrhage in stroma.

the time of admission, dehydration as well as cyanosis was evident. The heart was greatly enlarged, and a systolic murmur was audible over the precordium. There were rales over the bases of both lungs. The white blood cell count was 10,000 per cubic millimeter. During the 16 hours in the hospital the child did not urinate. He passed a voluminous watery dark

brown stool which gave a positive reaction for occult blood. He received oxygen, a digitalis preparation and a subcutaneous infusion of 2.5 per cent dextrose solution, as well as penicillin, sulfadiazine and streptomycin. He died in extreme cyanosis.

The autopsy confirmed the diagnosis of congenital heart malformation, which proved to be a complete transposition of the great vessels combined with a high interventricular septal defect. There were pulmonary edema and congestion and severe passive congestion of the liver. The kidneys were slightly enlarged and appeared mottled with alternating hemorrhagic and pale gray areas throughout the cortex.

Histological examination showed a picture of confluent widespread areas of advanced necrosis of all cortical elements and focal streaky hemorrhages, almost indistinguishable from that seen in cases 1 and 2 (fig. 7). Dilatation and fibrinoid necrosis of the intima of the interlobular and afferent arteries were present.

CASE 4.—L. K., a 7 month old boy, had passed bloody stools five days before admission and had had no bowel movements thereafter. His abdomen was distended, and a mass was palpable in the right lower quadrant. After the usual measures to hydrate the patient and to

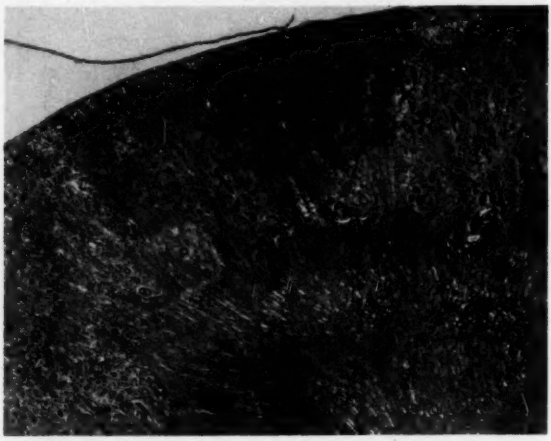

Fig. 7 (case 3).—Low power view of kidney. Note irregular band of confluent dark necrotic tissue in cortex and narrow strip of intact peripheral zone.

decompress the abdomen a laparotomy was performed and an ileocolic intussusception was reduced with considerable difficulty. The patient was in profound shock after the operation. The abdominal distention recurred; cyanosis developed, and in spite of blood transfusions and administration of oxygen and fluids, death ensued 30 hours later.

The autopsy showed gangrene of the cecum in the area of the earlier intussusception. There were also focal hemorrhages in the mucosa of the stomach and the distal part of the colon. Both lungs were collapsed. The kidneys were flabby but grossly not otherwise unusual.

The microscopic picture was one of advanced necrosis of the tubules in extensive confluent areas throughout the cortex, accompanied with streaky periarterial hemorrhages (fig. 8*A*). The glomeruli were dilated and often showed karyorrhexis and fading of the nuclei. The interlobular and afferent arterioles were dilated and frequently had smudgy edges and poorly staining walls, indicative of early necrosis (fig. 8*B*).

CASE 5.—G. S., a 7 month old boy had had cough and fever for several weeks and was finally admitted because of a swelling in the neck. He appeared critically ill, feverish and comatose. There was purulent drainage from the left ear. The neck was rigid, though the spinal fluid was normal. The white blood cell count was 30,000 per cubic millimeter. The

hemoglobin concentration was only 6.1 Gm. per 100 cc. The urine was acid, was brown and contained large amounts of albumin and numerous red and white corpuscles. Although the infant continued to void, no further specimens were obtained. The patient remained in coma, the pulse was irregular, vomiting occurred from time to time, liver and spleen became palpable and death took place four days after admission. The treatment had been chiefly supportive except for the administration of sulfadiazine.

Postmortem culture of the heart blood yielded a coagulase-positive Staph. pyogenes var. aureus. A bilateral purulent otitis media was present. Liver and spleen were enlarged. The

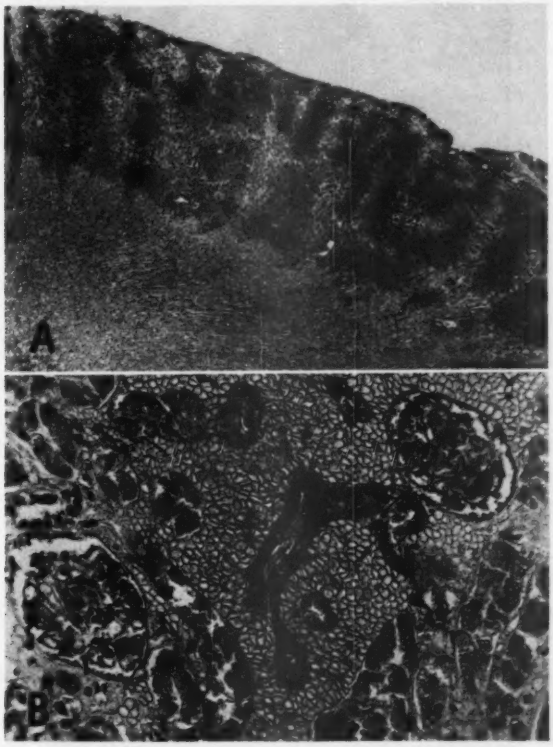

Fig. 8 (case 4).—*A*, low power view of kidney. Alternation of necrotic and hemorrhagic areas produces a peculiar mottled, streaky pattern. *B*, necrosis of tubules and glomeruli. A small artery undergoing early necrosis is shown surrounded by characteristic zone of fresh hemorrhage.

kidneys weighed more than twice as much as normal and were dark purple. The cut surface had a parboiled appearance, with small beefy red areas scattered through the dark hemorrhagic cortical tissue. The renal vessels were patent.

Microscopic examination showed almost complete obliteration of the renal cortex by necrosis and hemorrhage. In most areas the original elements could barely be recognized as shadow-like structures, but here and there the necrosis was of more recent appearance. Vascular lesions far more striking than in the first four cases were present throughout, involving again the interlobular and afferent arteries. The lumens of these vessels contained

fibrinoid material and sometimes platelet thrombi, and the intima and media had undergone necrosis, usually accompanied with an intense infiltration with leukocytes (fig. 9). The larger branches of the renal arteries and the veins were intact. No bacteria could be found in appropriately stained sections of the kidneys.

CASE 6.—J. B., a 6 week old girl, was admitted because of vomiting and diarrhea. She did not at first appear ill or dehydrated. The only abnormal finding was enlargement of the liver. The white blood cell count was 14,200 per cubic millimeter. Urinalysis revealed no abnormalities. Treatment consisted in administration of fluids and calcium gluconate, sulfadiazine sodium solutions by the intravenous route and injections of penicillin. Jaundice was noted one week after admission; the stools became clay colored, and the patient was losing weight. The abdomen became distended; stools and vomitus were blood tinged. The urine the day prior to death was normal, but in the last 24 hours the patient voided only twice. She died 10 days after admission.

The postmortem culture of the heart blood 16 hours after death yielded colon bacilli. The intestine was markedly distended. Severe pneumatosis was present in both ileum and colon. There were scattered hemorrhages in the wall in the vicinity of the emphysematous areas. The liver was enlarged, fatty and icteric. The kidneys were not grossly unusual.

The histological study of the liver showed acute inflammatory changes in the portal tracts together with proliferation of pseudocanaliculi and inspissation of bile thrombi between the

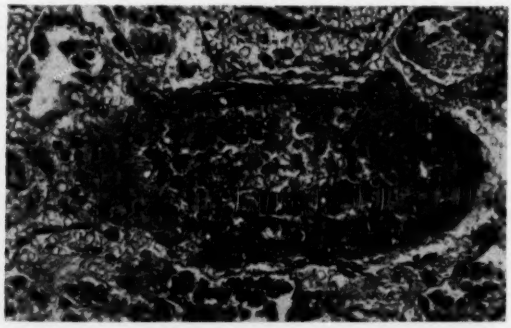

Fig. 9 (case 5).—Interlobular artery, showing necrosis and infiltration of intima, media and adventitia with inflammatory cells. Hemorrhage and edema of interstitium and beginning necrosis of tubules.

parenchymal cells. In the kidneys the picture was one of extensive confluent necrosis and patchy hemorrhage throughout the cortex. Except for the absence of visible alterations in the vessel walls, the appearance was indistinguishable from that seen in the preceding cases.

CASE 7.—M. B., a 2 day old premature boy, underwent an operation for imperforate anus. His condition was good until five days later, when diarrhea developed. In spite of immediate treatment with parenterally administered fluids, sulfadiazine sodium and blood transfusions, the child's condition deteriorated steadily. He appeared dehydrated; the skin was mottled, and chemical tests indicated acidosis. A single urine specimen, obtained in the fifteenth day of life, contained albumin and a moderate number of leukocytes. However, the blood urea nitrogen level at this time was only 16.8 mg. per 100 cc. Thereafter, the urine became scanty, and the patient died on the eighteenth day of life.

The autopsy disclosed a rectourethral fistula. There was evidence of severe malnutrition. Minimal bronchopneumonia was present, and a recent thrombus occluded the sagittal dural sinus. On microscopic examination a diffuse acute and subacute gastritis was observed.

The kidneys seemed grossly normal. In sections, however, extensive necrosis of cortical tubules was seen. The process was not as advanced as in the preceding cases. The epithelium in the majority of the convoluted tubules had lost its nuclei, and the cytoplasm was granular and deeply acidophilic, while the brush borders were no longer visible. In the loops of

Henle and the distal convoluted tubules the necrosis was somewhat less marked. A narrow zone beneath the cortex had escaped the process altogether. The glomerular capillaries were tremendously engorged, and occasional loops contained fibrin thrombi but rarely showed early necrosis. There were widespread streaky hemorrhages throughout the cortex. The small arteries were extremely dilated but appeared structurally intact.

CASE 8.—M. Y., a 6 week old boy who had been treated for "pyelitis" two weeks earlier, was admitted because of fever, diarrhea and sudden onset of cyanosis. He was listless and

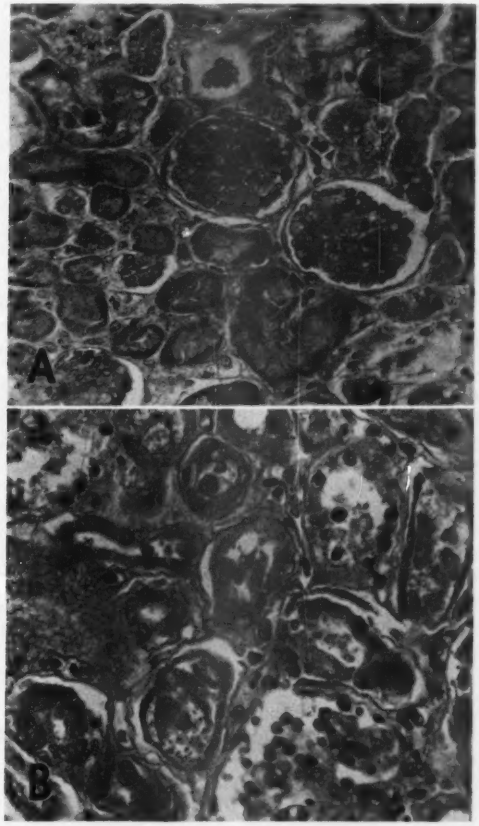

Fig. 10.—*A* (case 9), an early stage of the process. Glomeruli still intact. Early necrosis involving especially the convoluted tubules, which appeared deeply acidophilic in stained sections. The nuclei are lost or deeply pyknotic. *B* (case 10), advanced necrosis and reappearance of flat epithelial cells beneath sloughing tubular lining.

appeared seriously ill. The liver was palpable. Rales were heard over both lung fields. The urine contained albumin and many granular casts. During a diagnostic lumbar puncture respirations temporarily ceased, but the patient was quickly resuscitated. He received oxygen, intravenous infusions of whole blood, plasma, dextrose and salt solutions and sulfadiazine sodium by mouth. The diarrhea persisted, and edema developed. There was complete suppression of urinary secretion two days after admission, and the patient died on the third hospital day.

The autopsy showed massive terminal aspiration of stomach contents, an early aspiration pneumonia and edema of the gastrointestinal tract and the extremities. The kidneys were of normal size and gross appearance. The microscopic picture was identical with that described in case 7.

CASE 9.—D. K., a 1 day old infant born at term by face presentation after prolonged difficult labor, had breathed poorly since birth and had become definitely cyanotic at 12 hours of age. The temperature had risen to 105 F., and convulsions had occurred. Physical examination revealed ecchymoses of face and neck, mottling of the skin, poor quality of heart tones and femoral pulses and flaccid extremities. The infant was given oxygen, digitalis and sulfadiazine sodium. He died eight hours after admission.

At autopsy extensive pulmonary atelectasis was found, as well as marked congestion of brain, lungs and abdominal viscera. The renal cortices were quite pale, contrasting strikingly with the engorged medullary portions. Histologically, only a narrow band of superficial cortical tissue appeared intact. Throughout the remainder the cortical tubules, chiefly in their convoluted portions, had undergone necrosis. The collecting tubules appeared intact. In contrast to the preceding eight cases, the renal tubules still showed good cytoplasmic detail, though the nuclei were lost or fading or pyknotic (fig. 10 *A*). The intense acidophilia of the cytoplasm in the affected tubules contrasted strikingly with the more basophilic staining of the few intact elements and collecting tubules. The glomeruli and the arteries were not remarkable, either as regards structure or the state of filling of the lumens.

CASE 10.—L. A., a prematurely born infant who had done well for five weeks, suffered a rat bite and was given prophylactic injections of penicillin and tetanus antitoxin. Thereafter, he failed to gain weight, and he was admitted at 2 months of age. Except for the obvious poor nutritional condition, the findings on admission were negative. The urine contained a trace of albumin.

Under observation it became apparent that the patient had a moderately severe diarrhea. He received treatment for dehydration and acidosis and was given sulfadiazine. One week later the urine began to contain albumin, casts and red and white corpuscles. These findings persisted for approximately two weeks, and the urine was always acid but had an adequate specific gravity. The blood urea nitrogen level was moderately elevated. Diarrhea and weight loss continued, and the temperature was irregularly elevated. Eventually the urine cleared of abnormal elements, but in the third week the specific gravity was consistently low, 1.005. Unfortunately, no further urinalyses were carried out. The general condition deteriorated gradually. On the thirty-first day cyanosis developed suddenly, and the infant died two hours later.

The gross findings at autopsy were meager, consisting in evidence of malnutrition, hypostatic pneumonia and a small subarachnoid hemorrhage. The kidneys were of normal size but very pale. Microscopically, widespread necrosis of the tubules was seen throughout the cortex. The process appeared to be less recent than in any of the previous cases. Along with necrosis, sloughing of tubular epithelium and formation of granular and cellular casts, one could see pictures suggestive of regeneration, with flat atypical tubular epithelium and irregular vesicular nuclei (fig. 10 *B*). Mitotic figures were not found, however. Many glomeruli showed hemorrhage into the capsular spaces and lumens of adjacent tubules, though no necrosis or thrombosis of the capillary loops could be demonstrated. No vascular lesions were visible.

CASE 11.—S. P., a 12 year old girl, had been operated on unsuccessfully in early infancy for a meningocele. Hydrocephalus, incontinence of bladder and rectum and clubbing of both feet had developed, and, more recently, extensive trophic ulcers had appeared over the sacrum and the lower extremities. The patient was admitted in critical condition because these ulcers had become infected. There was widespread phlegmonous inflammation accompanied with a malodorous discharge. The white blood cell count was 15,000 per cubic millimeter. A urine specimen could not be obtained because the patient was incontinent. Treatment consisted in administration of sulfadiazine and supportive measures. The child soon began to vomit and at the end of one week lapsed into coma. The blood pressure at this time was 120/40. The blood urea nitrogen level was 84 mg. per 100 cc. The urine, obtained at that time by catheter, contained albumin and cellular casts. The patient died eight days after admission.

At autopsy extensive undermining ulcers were observed to be present over the lower half of the body. The spinal cord appeared intact. There was internal hydrocephalus. A severe fibrinous cystitis was present. The kidneys were flabby and muddy yellow-gray but not enlarged. On microscopic examination complete necrosis of virtually all of the cortical tubules was evident. Numerous small streaky hemorrhages were scattered throughout the cortex. The interlobular arteries as well as veins were dilated, but structural changes in their walls could not be seen, and there was no thrombosis.

COMMENT

Pathologically, all but two cases (cases 9 and 10) conformed to the fully developed, classical picture of symmetrical cortical necrosis. In case 9 an earlier stage of the lesion was represented. The tubules showed increased acidophilia of the cytoplasm, loss of detail and fading or complete loss of the nuclei but had not yet undergone complete necrosis, and the glomeruli appeared as yet intact. As in the more advanced cases, a very narrow strip of cortical tissue immediately beneath the capsule had remained intact, presumably because of anastomoses to the vessels of the capsules.[1]

Case 10 differed somewhat in that regeneration of tubules seemed to have occurred. The combination of hemorrhages into the capsular spaces of many glomeruli, necrosis and sloughing of nearly all the cortical tubular epithelium and signs of epithelial regeneration suggests that the ischemic injury to the renal parenchyma was less severe or less prolonged than in the majority of cases and permitted survival and beginning restitution. This interpretation is in keeping with the development of hematuria and albuminuria early in the patient's illness followed by clearing of the urine of abnormal elements and lowering of the specific gravity. The renal lesion in this case might be expected to have healed completely if the patient had not succumbed to the persistent diarrhea. The existence of reversible forms of symmetrical cortical necrosis has been postulated by Duff and Murray.[1]

The gross pathological picture of cortical necrosis was less consistently developed in our cases than were the histological changes. In only 2 cases did the kidneys have the typical gross appearance of mottled dry yellow confluent areas forming a band through the cortex surrounded and interrupted by streaky hemorrhages. In three instances diffuse or mottled streaky hemorrhages were seen grossly. In the others the kidneys appeared grossly normal or at most were somewhat enlarged, flabby or pale. Perhaps this frequent lack of striking gross abnormalities together with the difficulties of clinical diagnosis have prevented recognition of the condition in this age group heretofore.

In any event, our experience suggests that symmetrical cortical necrosis is not a particularly rare disease of the kidney in infancy and, in fact, that the infantile kidney may be particularly susceptible to the development of this lesion. Cortical necrosis probably represents the commonest single cause of renal insufficiency in this age group.

The absence of a consistent clinical picture has already been discussed. It is apparent from the case histories that oliguria or anuria was frequently present for at least a day or two prior to death but was not appreciated in its true significance. The difficulties of interpreting oliguria, albuminuria or azotemia in a dehydrated infant with diarrhea or vomiting are apparent to every pediatrician.

Apart from urinary symptoms, abdominal distention was a frequent though not constant symptom. It is interesting to recall that marked gaseous distention of the intestine was observed by Trueta and his associates [3b] in rabbits in which symmetrical cortical necrosis was produced by the intravenous injection of a potent Staphylococcus toxin.

Campbell and Henderson [2] were struck by the simultaneous occurrence of vascular lesions in the kidneys and mesenteric circulation in their patient. They have stressed that diarrhea may be a symptom associated with damage to the mesenteric vessels due to the same cause as the renal lesion, rather than a primary event complicated by the renal injury. This interpretation would seem to fit our first case, in which arteritis and thrombosis were present in small branches of the superior mesenteric artery and gangrene and hemorrhage of the intestine had ensued. This was the only case, however, in which vascular lesions could be demonstrated outside the renal circulation.

In searching for a common etiological factor or pathogenetic mechanism, we were struck by the fact that in our case material a definite increase in incidence during the last two years of the study was evident. There were no cases prior to 1943, two cases in 1943 and one case in 1944. After an interval of four years there were seven cases of symmetrical cortical necrosis in infants studied at autopsy in the two year period 1948 to 1949. Since the quality and methods of pathological examination remained unchanged during the 10 year period, the recent sudden accumulation of cases is not likely to mean that formerly the condition was overlooked. The increase seems to be a real one, though it remains to be seen whether the trend continues. No major change in the routine care of infants took place in this hospital during the two years in question. The introduction of sulfonamides and penicillin came some time before, and the more recent antibiotics were not used for the majority of the patients described here. Electrolyte and fluid therapy was not modified during these two years. The significance of the sudden increase remains a mystery at present. A discussion of therapeutic management is beyond the scope of this paper.

SUMMARY

Pathological examination disclosed 11 cases of symmetrical cortical necrosis among 2,058 autopsies on infants and children. Ten of the patients were infants ranging from 1 day to 7 months in age. Among the precipitating factors of possible etiological significance, diarrhea with dehydration was the commonest. In addition, a variety of other conditions, sometimes associated with severe shocklike states, was encountered. Symmetrical cortical necrosis is reported for the first time in the newborn infant and for the first time in association with erythroblastosis fetalis.

The clinical signs of renal disease were often inconspicuous, and the condition was rarely suspected during life. An accurate diagnosis was never made. Oliguria, albuminuria, hematuria and azotemia were the chief positive findings.

The mechanism of renal cortical necrosis seems to reside in ischemia produced by structural or functional changes in the small intrarenal arteries and arterioles. The histological picture in the majority of the cases indicated total renal insufficiency, but in one instance a reversible lesion with signs of restitution was thought to be present. Symmetrical cortical necrosis may prove to be the commonest cause of renal insufficiency in infancy. A sudden unexplained increase in the number of cases was observed during the last two years of the 10 year study.

II. ACUTE GLOMERULAR THROMBOSIS

WOLF W. ZUELZER, M.D.

UNDER the term acute glomerular thrombosis we report briefly two cases that have certain similarities to the cases of symmetrical necrosis in that the intrarenal blood flow is interrupted but differ from them in that the site of the circulatory obstruction is clearly in the glomeruli and the mechanism consists in the formation of thrombi in the glomerular capillary loops. The condition, which seems to represent a complication of certain severe bacteremias and appears to depend on the presence of micro-organisms within the glomerular capillaries, has received little attention since Blackman and Rake [1] described it under the title "acute pneumococcal nephritis." One of the cases (case 4) reported as symmetrical cortical necrosis in a young infant by Campbell and Henderson [2] seems to fall in this category.

Since the renal lesion is associated with severe infection, the development of clinical manifestations is often cut short by death of the patient from the overwhelming primary illness. If the period of survival is long enough, the picture of renal insufficiency may develop rapidly and may itself become the lethal factor. The first case illustrates the development of the clinical picture in a young infant. The second case presents an example of overwhelming infection with death occurring before the renal lesions became clinically apparent.

REPORT OF CASES

CASE 12.—E. J., a 3 week old infant, was admitted because of severe gangrenous inflammation of the entire penis following circumcision. Physical examination disclosed, in addition to the genital lesion, an area of redness about the umbilicus. The nasal passages were filled with purulent exudate. The child's general condition was regarded as fair. The temperature was normal. The white blood cell count was 40,000 per cubic millimeter, with a differential count of 62 per cent neutrophils. The blood culture was sterile, but the patient had already been treated with injections of penicillin before admission to the hospital. The first urine specimen was not obtained until two days later. It contained albumin (2+) and numerous red corpuscles and leukocytes. The blood urea nitrogen concentration on the following day was 52.9 mg. per 100 cc. The treatment consisted in blood transfusions, injections of penicillin and sulfadiazine sodium and, on the last day before death, streptomycin. The general condition of the infant deteriorated. He had attacks of cyanosis and was placed in an oxygen tent. On the third hospital day anuria developed, and on catheterization the bladder was found empty. The patient died on the fourth day after admission.

The autopsy disclosed massive pulmonary hemorrhage as the immediate cause of death. The penis was gangrenous throughout. Small thrombotic sterile verrucae were present on the aortic and mitral valves in the absence of any cardiac malformation. There was an acute splenitis.

The kidneys were studded with petechiae. Microscopically, every glomerulus was completely obstructed by fibrin thrombi (fig. 1). Many of the capillary loops and sometimes entire glomeruli were necrotic. Hemorrhage had occurred frequently into the capsular spaces and

1. Blackman, S. S., and Rake, G.: Acute Pneumococcal Nephritis, Bull. Johns Hopkins Hosp. **51**:217, 1932.

2. Campbell, A. C. P., and Henderson, J. L.: Symmetrical Cortical Necrosis of the Kidneys in Infancy and Childhood, Arch. Dis. Childhood **24**:269, 1949.

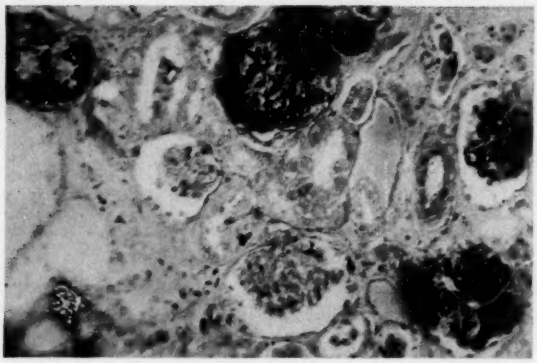

Fig. 1 (case 1).—Fibrin stain of kidney, showing casts of fibrin thrombi in glomerular capillaries.

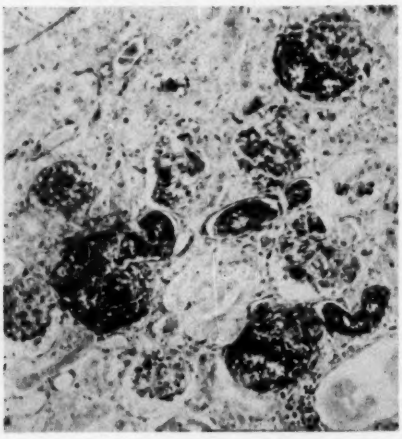

Fig. 2 (case 1).—Hematoxylin-eosin stain, showing hemorrhage (dark masses) into capsular spaces of glomeruli and lumens of adjacent tubules.

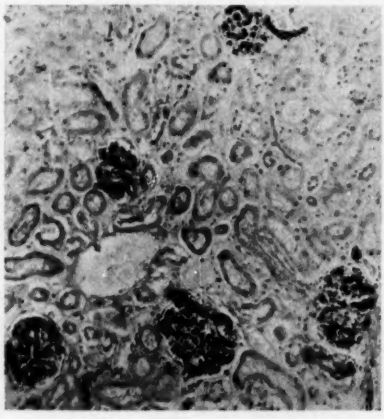

Fig. 3 (case 2).—Fibrin thrombi occluding glomerular capillaries.

adjoining tubules (fig. 2). The tubules, apart from the occasional distention with blood, showed degenerative changes and occasionally necrosis. The blood vessels appeared intact. Microorganisms could not be demonstrated, possibly because chemotherapy had been administered to the patient for five days prior to death.

CASE 13.—W. W., a 7 month old infant, was admitted because of fever and convulsions of a few hours' duration. The illness had begun with lethargy and irritability three days earlier. A physician had prescribed pills of unknown composition. The infant was semicomatose and critically ill. The temperature was 105 F. Pneumococcus type 18 was isolated from both the spinal fluid and the blood. Pneumococci were so numerous that they could be seen easily in ordinary films of peripheral blood. The patient received one injection of penicillin and died within a few hours after admission.

The autopsy revealed a purulent meningitis. The kidneys appeared grossly normal. Microscopically, every glomerulus was plugged by fibrin thrombi (fig. 3). Within the capillary loops innumerable lancet-shaped diplococci, evidently pneumococci, were readily seen (fig. 4). The

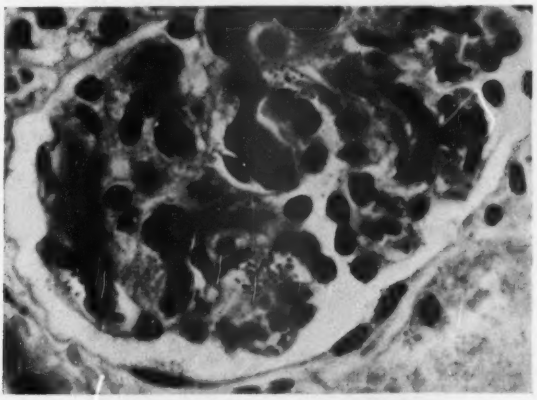

Fig. 4 (case 2).—High magnification of glomerulus, showing numerous diplococci and fibrin casts.

glomerular capillaries, in contrast to those in the preceding case, were still intact, and as yet there was no bleeding into the capsular space and no secondary change had developed in the tubular epithelium. The patient died before such changes had time to develop.

SUMMARY

Two cases of acute generalized glomerular thrombosis in young infants with severe extrarenal infections are briefly reported. The process seems to depend on the presence of organisms in the glomerular capillaries and as a rule is clinically cut short by the overwhelming effects of the systemic infection. If the patient survives the initial phase of such an infection, the obstruction of the glomerular circulation leads to hematuria, anuria and azotemia. Since overwhelming infections can now be dealt with more successfully than in the past, and the patients are likely to survive, the renal complication of glomerular thrombosis may become of greater clinical importance than heretofore.

III. ARTERIOLAR NECROSIS (ACUTE MALIGNANT HYPERTENSION)

WOLF W. ZUELZER, M.D.

ARTERIOLAR necrosis of the kidneys is a lesion found characteristically in malignant hypertension. To our knowledge this condition has not been previously reported as occurring in infancy.

Our case material includes two cases of arteriolar necrosis. One of these, case 14, has been reported elsewhere in detail.[1] This was an instance of a peculiar glomerulonephritis in an 8 year old boy who after nephrectomy for an embryoma of one kidney had received intensive radiation therapy over an area that included the remaining kidney. He had died with signs of hypertension and renal failure. The glomeruli were found to be obliterated, and the tubules, dilated and atrophic, and the arterioles throughout showed fibrinoid necrosis and often were surrounded

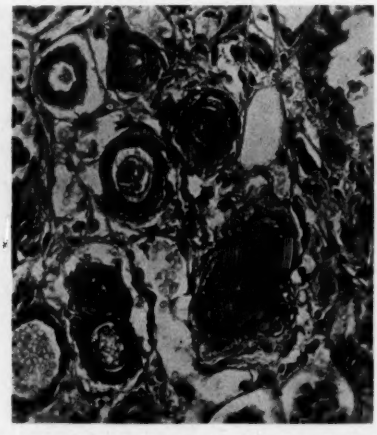

Fig. 1.—Cross section of several renal arterioles, showing fibrinoid deposits in the intima, blurring of contour and variable degrees of necrosis.

by small hemorrhages. The vascular changes were interpreted as secondary to the combination of hypertension and uremia resulting from the severe generalized glomerular obstruction.

The second case in this group concerns an infant and warrants a more detailed presentation.

REPORT OF A CASE

CASE 15.—The patient was a 1 year old Negro girl admitted because of facial edema of one week's duration. The past history was entirely negative. Approximately one month before the onset of her symptoms the patient had received an injection of diphtheria antitoxin. Although she had experienced no immediate reaction, a transient swelling of the arm which was the site of the injection had occurred a week later.

The examination disclosed an acutely ill, pale child with generalized edema. The heart was enlarged to the left, and a loud systolic murmur was audible over the precordium. The

1. Zuelzer, W. W.; Palmer, H. D., and Newton, W. A., Jr.: Unusual Glomerulonephritis in Young Children, Probably Radiation Nephritis?: Report of 3 Cases, Am. J. Path. **26**:1019, 1950.

pulse rate was rapid, and the blood pressure was 148/94 mm. Hg. Liver and spleen were palpable. The urine was smoky and contained large amounts of albumin, numerous red corpuscles, leukocytes and granular and hyaline casts. The hemoglobin concentration of the blood was only 2.0 Gm. per 100 cc. The nonprotein nitrogen was 85 mg. per 100 cc.

The patient was given repeated blood transfusions and intramuscular injections of magnesium sulfate. The hemoglobin level rose, but the blood pressure failed to return to normal; in

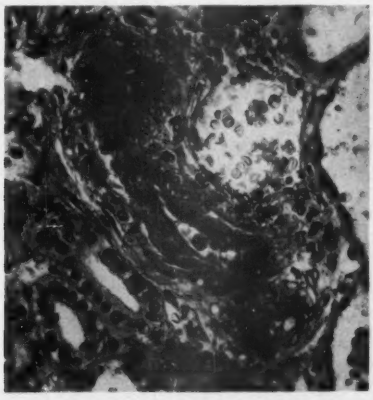

Fig. 2.—Longitudinal section of renal arteriole, showing extensive necrosis.

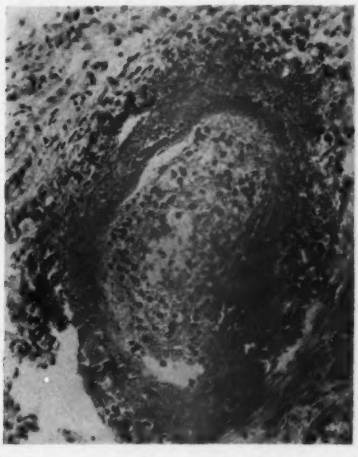

Fig. 3.—Artery in wall of uterus, showing necrosis of intima and media and inflammatory reaction. The picture is that of periarteritis nodosa.

fact, it continued to rise, reaching a peak of 200/110 mm. Hg. Gallop rhythm and progressive cardiac enlargement developed and were accompanied by dyspnea, abdominal distention, vomiting and finally convulsions. The urine remained unchanged. The patient died 12 days after admission, three weeks after the onset of symptoms.

The kidneys were slightly enlarged and were studded with minute hemorrhages. The heart showed left ventricular hypertrophy. An extensive bronchopneumonia was present.

The outstanding microscopic observation was the universal necrosis of the arterioles of the kidneys (figs. 1 and 2). The process seemed to begin as a fibrinoid, edematous change in the intima, with formation of thick rings of deeply staining material that tended to narrow the lumen. The usual more advanced lesion involved the entire thickness of the wall, which was necrotic, was infiltrated with fibrin and had a blurred, smudgy contour. Occasional red blood corpuscles infiltrated the media or formed small extravasations in the adventitia. There was no inflammatory cell infiltration.

Many glomeruli had undergone acute fibrinoid necrosis and hemorrhage. Occasionally the capillary loops contained fatty material. Rarely, a marginal proliferation of capsular epithelium had led to the formation of small crescent-like structures. The vast majority of the glomeruli, however, appeared normal but completely bloodless and collapsed. The tubules were often somewhat dilated, especially when filled with blood from adjacent hemorrhagic glomeruli, and focal areas of acute degenerative changes and even necrosis were seen, but on the whole the tubular apparatus was intact.

No vascular lesions comparable to the arteriolonecrosis in the kidneys were observed in other organs, but an acute necrotizing arteritis, characterized by medial necrosis and inflammatory exudate in and about the adventitia, was present in small arteries of the uterus, bladder, esophagus and pancreas. The picture of these lesions was that of periarteritis nodosa (fig. 3).

COMMENT

The interpretation of this unique case is of necessity a matter of speculation because a basis for comparison is lacking, at least in the age group of the patient. In contrast to the preceding case, primary disease of the kidneys, such as glomerulonephritis, was not demonstrable. The lesions of the renal arterioles were those of acute malignant hypertension.[2] The component of a cellular inflammatory reaction was completely absent. On the other hand, an inflammatory type of arteritis indicative of a sensitivity reaction was present in arteries of other parts of the body.

Hypertension is now generally regarded to be the cause, not the effect, of renal arteriolar necrosis. Renal vascular lesions identical with those seen in human malignant hypertension have been produced experimentally by a variety of methods, most recently by Masson, Hazard, Corcoran and Page.[3] These authors observed arteriolar necrosis in the kidney of rats after injection of desoxycorticosterone and crude anterior pituitary extracts and after wrapping of the kidneys with silk. They concluded that the common pathway of arterial damage produced by these three different methods is arterial hypertension.

In our case the presence of a second type of vascular lesion, periarteritis nodosa, in larger extrarenal vessels suggests a plausible mechanism for the development of hypertension. According to this interpretation, a state of vascular hypersensitivity developed, probably as the result of the injection of horse serum. The development of vascular lesions of the periarteritis type was associated with hypertension which in turn led to renal arteriolonecrosis. The time interval between the injection of antitoxin and the development of symptoms fits this assumption. Unfortunately, the autopsy was restricted in extent so that a possible cerebral or pituitary mechanism could not be excluded. Our hypothesis seems to fit the observed facts and is in accord with current concepts regarding renal vascular disease.

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2. Anderson, W. A. D.: Pathology, St. Louis, C. V. Mosby Company, 1948.

3. Masson, G. M. C.; Hazard, J. B.; Corcoran, A. C., and Page, I. H.: Experimental Vascular Disease Due to Desoxycorticosterone and Anterior Pituitary Factors: II. Comparison of Pathologic Changes, Arch. Path. **49**:641 (June) 1950.

SUMMARY

Renal arteriolar necrosis was observed in two patients. In one case it was regarded as a complication of an unusual severe type of glomerulonephritis. In the second patient, a 1 year old infant, the renal arteriolar necrosis was not associated with primary disease of the kidney. The picture was identical with that of malignant hypertension in the adult. Because of the presence of lesions of periarteritis nodosa in other parts of the body, the case was interpreted as an example of vascular hypersensitivity with hypertension, leading to the development of the clinical picture of renal insufficiency and the pathological picture of renal arteriolar necrosis. The clinical differentiation from acute glomerulonephritis was difficult, but the complete failure of magnesium sulfate to influence the blood pressure might have provided the clue to the presence of organic vascular disease.

IV. OCCLUSION OF THE RENAL ARTERY

WOLF W. ZUELZER, M.D.
RUBEN KURNETZ, M.D.
and
WILLIAM A. NEWTON Jr., M.D.

FEW REFERENCES concerning occlusion of the renal arteries by embolism or thrombosis in infants can be found in the recent literature. Gross [1] reported two such cases in 1945 and pointed out that arterial embolism and thrombosis in infancy are likely to be commoner than indicated by the number of published cases. Morrison [2] in the same year described total ischemic infarction of one kidney in an infant with thrombosis of the abdominal aorta ascribed to a peculiar arteritis.

Blockage of a renal artery leads to albuminuria and passage of blood and casts in the urine. Azotemia, oliguria and anuria and uremia will follow if both renal arteries are affected. The diagnosis of arterial occlusion of the kidneys is difficult unless emboli with resultant infarction appear in the extremities.

Our material contains, in addition to cases of localized infarcts secondary to bacterial endocarditis, five instances of total renal infarction due to blockage of one or both renal arteries. Four of the patients were newborn infants. In one of these the infarction was bilateral.

The general clinical picture in the four newborn infants was not uniform. The symptom of diarrhea was of prime concern in two patients; exfoliative dermatitis was the reason for the admission of the third. The fourth infant had symptoms referable to massive cerebral hemorrhage, due presumably to embolism from the same source as that affecting the kidney. The total duration of the illness was less than five days in each case. Hematuria was observed in two patients, while the two other patients had melena, though bloody urine was not noted. Azotemia was present in two of the patients. In one of the infants (case 16) gangrene of the toes occurred as the result of arterial embolism; in another patient the femoral pulse could not be palpated as the result of thrombosis of the abdominal aorta.

1. Gross, R. E.: Arterial Embolism and Thrombosis in Infancy, Am. J. Dis. Child. **70**:61 (Aug.) 1945.

2. Morrison, J. E.: Thrombosis of the Aorta in the Newborn: 3 Cases, One with Infarction of the Liver, J. Path. & Bact. **57**:221, 1945.

The pathological examination disclosed aneurysm and thrombosis of the ductus arteriosus as the source of the embolism in two cases. In one instance (case 17) thrombosis of the descending branch of the coronary artery, as well as of the entire lower abdominal aorta and of the sagittal dural sinus, was seen, in addition to total hemorrhagic infarction of both kidneys. The process in all these vessels appeared to be of the same age.

The fifth case of arterial occlusion occurred in a 2 year old boy and was due to compression and kinking of the left renal artery by tumor masses invading the retroperitoneal space from a neuroblastoma of the adrenal gland. The left renal vein was also occluded by thrombosis. The opposite kidney had remained entirely

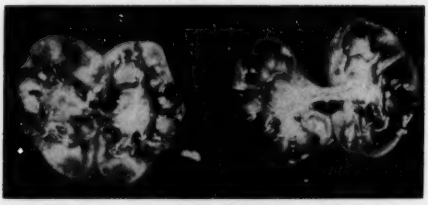

Fig. 1 (case 16).—Ischemic and hemorrhagic infarction of both kidneys.

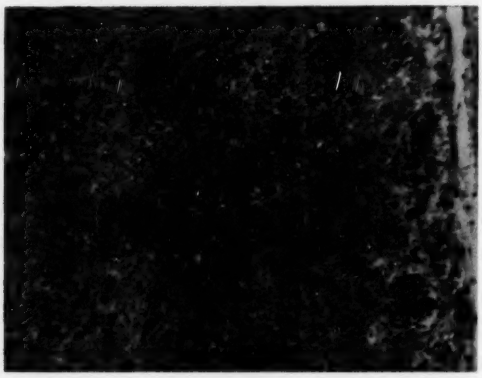

Fig. 2 (case 16).—Microscopic appearance of renal cortex. Hemorrhagic destruction is complete in this area.

normal, and no symptoms referable to the destruction of the left kidney had been noted. Death was due to the effects of the widely disseminated neoplasm.

REPORT OF CASES

CASE 16.—G. R., a 1 week old Negro girl, was admitted because of weight loss and diarrhea and vomiting since the third day of life. She appeared acutely ill and poorly nourished. The skin showed sclerema. The white blood cell count was 28,700 per cubic millimeter. In spite of the usual treatment for diarrhea and dehydration, the progress of the illness was adverse. Generalized edema developed; the respirations became labored, and generalized convulsions occurred. On the second day it was noted that the fourth toe on the left foot was becoming discolored. As the patient had not yet voided, the bladder was catheterized, but only 3 cc. of urine was obtained. This specimen contained large amounts of albumin and a few red corpuscles.

The blood urea nitrogen level was 140 mg. per 100 cc. Complete anuria developed. Several toes became gangrenous. Facial edema was extreme. Although peritoneal lavage was instituted, the patient died four days after admission.

The autopsy revealed a thrombus in the ductus arteriosus protruding into the aorta, where it had a rough, irregular edge suggesting that part of it had broken off. There was, however, no aneurysmal dilatation of the ductus. The lower abdominal aorta was occluded by a firmly attached thrombus, evidently of embolic origin, extending from the level of the renal arteries

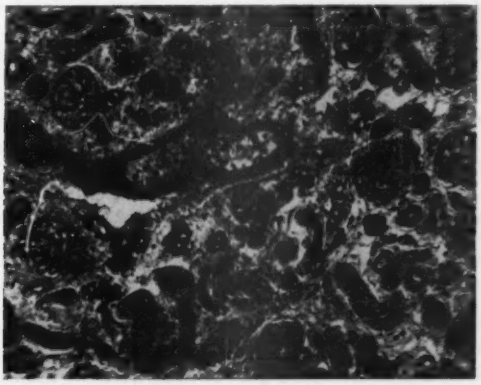

Fig. 3 (case 16).—Area showing ischemic necrosis. Note similarity to appearance of renal cortex in cases of symmetrical cortical necrosis.

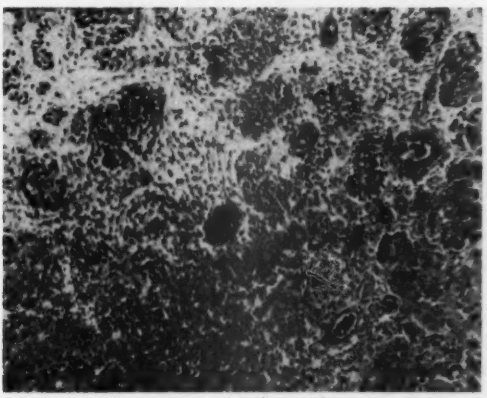

Fig. 4 (case 18).—Advanced necrosis of renal tissue.

to the bifurcation and continuing into the left iliac artery and through the femoral artery as far as the level of the knee. The left kidney was totally infarcted, hemorrhagic and friable. A brittle inelastic clot filled the lumen of the left renal artery. The right renal artery appeared patent, but the greater part of the right kidney was likewise infarcted, with hemorrhage or necrosis sparing only a few small areas (figs. 1, 2 and 3). In addition to these findings, an embolus was encountered in a large intrahepatic branch of the left hepatic artery, but there was no infarction of the liver. The terminal portion of the sagittal dural sinus was also occluded by a thrombus.

CASE 17.—C. E., a Negro boy 8 days of age, was admitted because of diarrhea of five days' duration. The patient exhibited cyanosis and lethargy. The amount of urine obtainable was so small that tests for albumin could not be made. The sediment contained many white corpuscles. Subsequently complete anuria developed. Generalized edema appeared 24 hours after admission, by which time only the customary amounts of fluids had been given parenterally. The abdomen became distended, and blood appeared in the stools. Anuria, edema and cyanosis persisted. The blood urea nitrogen was 49 mg. per 100 cc. The patient died four days after admission.

The autopsy disclosed thrombosis of the liver and abdominal aorta, extending from the renal arteries through the bifurcation into the left common iliac artery. Short branches of the main thrombus extended into both renal arteries. Both kidneys were hemorrhagic and friable throughout. The heart was enlarged; the left ventricle was dilated, and its apical portion was the seat of a fresh hemorrhagic infarct, secondary to thrombosis of the anterior descending branch of the left coronary artery.

CASE 18.—L. P. was a premature infant admitted immediately after birth in critical condition. After the administration of oxygen and external heat, the patient's condition improved temporarily, but shortly she began to vomit thick bile-stained mucus and passed tarry stools. Sclerema developed, the vomiting continued, and the child died on the fifth day of life. A single urine specimen, obtained on the third day, was normal.

At autopsy massive hemorrhage into the left frontal and parietal lobes of the brain was thought to have been the chief immediate cause of death. The ductus arteriosus was filled with a firmly attached thrombus and was dilated in the manner of an aneurysm. The right renal artery was occluded by an embolus, and the entire right kidney was infarcted, partly hemorrhagic and partly necrotic (fig. 4). The left kidney was intact.

CASE 19.—D. D. was admitted with a generalized severe exfoliative dermatitis at 6 days of age. Apart from the findings concerning the skin, a mass thought to be kidney was palpable in the left lower quadrant of the abdomen. The urine contained albumin (2+) and numerous red and a few white corpuscles. The patient died within 12 hours after admission.

The autopsy disclosed the presence of numerous small abscesses throughout both lungs, from which Staphylococcus pyogenes var. aureus and colon bacilli were grown on culture. The left kidney was greatly enlarged and weighed 60 Gm., as compared with 20 Gm. for the right kidney. The left kidney was necrotic throughout and partly hemorrhagic. Although the main stem of the left renal artery appeared patent, microscopic examination showed septic emboli containing many bacterial masses in the large and small arterial branches throughout the kidney. The right kidney appeared normal both grossly and microscopically.

COMMENT

Our experience confirms the view of Gross that arterial embolism and thrombosis are not particularly rare complications of early life. The primary site of arterial thrombosis may be the ductus arteriosus, as it was in two of our patients, in one of the patients reported on by Gross,[1] in a number of cases cited by this author and in a case described by Morrison.[2] The possibility of retrograde thrombosis from the umbilical arteries was stressed by Gross, but this condition was not encountered in our case material.

The association with thrombosis of a coronary artery in case 17 and of the dural sinus in case 16 suggests a common predisposing factor apart from purely local conditions, and the case histories of our patients indicate that extreme dehydration may be such a factor in the newborn, just as it is thought to be a factor in the development of venous thrombosis.

The clinical diagnosis is suggested by the urinary findings and azotemia in the newborn, especially if other signs of arterial embolism, such as gangrene of the extremities or suppression of the femoral pulses, can be demonstrated.

SUMMARY

The case histories of four newborn infants and of an older infant who were shown to have died with occlusion of one or both renal arteries are briefly presented. The condition is not as rare as the number of recorded cases seems to indicate. A frequent source of arterial embolism which may affect the kidneys in the newborn period is a thrombus of the ductus arteriosus. Dehydration may be a factor of etiological significance in the formation of the thrombus.

The clinical picture is characterized by abnormal urinary findings, a tendency toward anuria and azotemia and, sometimes, signs of embolism in other parts of the body.

V. ISCHEMIC ATROPHY OF THE KIDNEYS

WOLF W. ZUELZER, M.D.

THE EFFECTS of gradual or incomplete occlusion of the renal arteries or their branches are not as well known as are those of sudden complete blockage of the arterial circulation. Whereas the latter situation leads to acute necrosis and, if enough renal parenchyma is destroyed, to death of the organism, lower degrees of arterial obstruction may permit survival of tissue elements but in time will lead to atrophy and other retrogressive changes. In a recent paper, Christofersen and Hirsch [1] have called attention to this sequence of events which may result from a variety of pathological processes associated with gradual occlusion of intrinsic renal arteries. In such a kidney the nephrons decrease in size and ultimately revert to fetal characteristics. The loss of function of the atrophic nephrons leads to progressive renal failure and death in uremia.

One may postulate that the nephrons of a kidney in which the blood supply has always been marginal as a result of prenatal developmental processes or has become inadequate early in infancy will retain fetal characteristics and that such a kidney will present the picture of congenital hypoplasia. In this type of kidney one would expect the nephrons to be present in apparently normal numbers but the glomeruli to be small and the tubules to appear undifferentiated and to lack the characteristic brush borders, cytoplasmic granules and differences in height and staining properties of the epithelium. The following case report illustrates the effects of progressive interference with the circulation in such a hypoplastic kidney.

REPORT OF A CASE

CASE 21.[2]—A. P., an 8 year old boy, had been seemingly well until three days before admission, when he complained of dizziness, headache and vomiting. Shortly visual disturbances, convulsions and coma supervened. The physical examination disclosed the presence of a soft apical systolic murmur. The heart was not enlarged. The blood pressure was 225/125 mm. Hg. The femoral pulses were of good quality. The urine contained a trace of albumin and later, on one occasion, a few red and white corpuscles. The specific gravity ranged from 1.017 to 1.026. The blood urea nitrogen was slightly elevated.

The intravenous pyelogram showed good filling of the left renal pelvis with dye but no excretion on the right.

1. Christofersen, H. R., and Hirsch, E. F.: Bilateral Extensive Focal Ischemic Atrophy of the Kidneys, Arch. Path. **48**:548 (Dec.) 1949.

2. A more detailed clinical presentation of this patient appeared as case 3 in the Conference at the Children's Hospital of Michigan, J. Pediat. **36**:254, 1950.

With the patient under observation, the blood pressure remained elevated and could not be influenced by administration of piperoxan hydrochloride. The eyegrounds showed no change, however. The patient's condition became critical, with persistent coma and convulsions. A few days after admission the right kidney was removed. Within 48 hours, the blood pressure had fallen considerably and there was dramatic clinical improvement. The patient became rational. The urine became normal, and the blood urea nitrogen level fell to normal values. During the 10 month period elapsed thus far after the operation, the patient continued to do well clinically, but the blood pressure began to rise again and the intravenous pyelogram showed, instead of the expected compensatory hypertrophy, actual shrinking of the remaining (left) kidney.

Fig. 1.—Gross appearance of surgically removed kidney. Note hypoplasia and multiple infarcts.

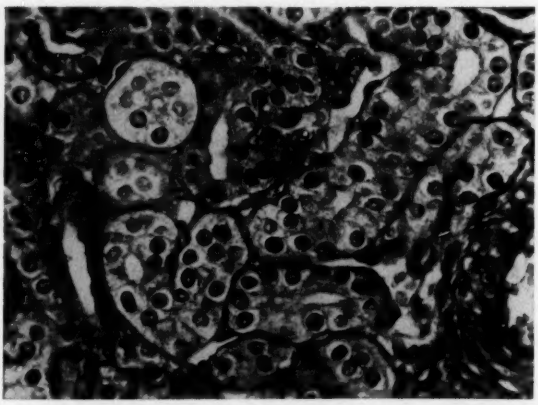

Fig. 2.—Representative field in the renal cortex, showing primitive appearance of convoluted tubules.

The right kidney, removed at operation, was markedly hypoplastic. It weighed only 24 Gm., which is the expected weight in a 5 month old infant rather than in an 8 year old boy. Interspersed throughout the bulk of grossly normal-appearing, smooth pink tissue were many fresh yellow ischemic wedge-shaped infarcts (fig. 1) in the cortex, as well as in the medulla.

The microscopic picture was no less striking. In the infarcted areas all tissue elements were necrotic. A few of the interlobar arteries were occluded by fresh thrombi. There was no duplication of the elastica or intimal thickening of the arteries anywhere.

The areas which had escaped infarction were composed of intact but small glomeruli, corresponding approximately to those of a 1 year old infant, and of tubules which had a uniformly

primitive appearance (fig. 2). They resembled collecting tubules rather than portions of the functioning nephrons. The cytoplasm was clear and nongranular; brush borders were not developed; the height of the epithelium was fairly uniform, as was the staining reaction of the cytoplasm. The lumens were patent. Here and there a diffuse increase in connective tissue stroma was notable.

COMMENT

The picture presented by the kidney in this case was one of general atrophy or, more properly speaking, lack of growth and differentiation of the nephrons, the anlage of which evidently had developed normally, since their number was apparently normal. The structure of the nephrons was in keeping with their observed functional inferiority.

The chronic marginal ischemia which could explain this picture must have been present since early infancy, if not earlier, because the growth of the kidney had not progressed beyond the stage normally seen in the young infant. The presence of fresh ischemic infarcts lends weight to the assumption that the hypoplasia had its basis in a vascular process and at the same time indicates that the process was still active. Moreover, the recurrence of hypertension and the observed shrinkage of the contralateral kidney after the operation tend to prove that the process was bilateral and continuing to be active. Unfortunately, the technic of nephrectomy used in this case precluded observation of the renal artery *in situ*. In view of the presence of a cardiac murmur, and in the absence of structural changes in the vessels of the surgically removed kidney capable of explaining the ischemic atrophy, a process of repeated embolization, secondary to a nonbacterial thrombotic endocarditis on the basis of congenital heart disease, seems to offer the likeliest explanation at this time.

SUMMARY

A case of renal hypoplasia associated with multiple fresh ischemic infarcts in a child suffering from hypertension and beginning renal failure is presented. The hypertension recurred after temporary dramatic relief from nephrectomy, and roentgenograms showed progressive shrinking of the remaining kidney. The renal changes are interpreted as evidence of chronic marginal ischemia due to incomplete arterial blockage, permitting survival but preventing growth and differentiation, and thus adequate function, of the nephrons.

VI. THROMBOSIS OF RENAL VEINS

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and
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IT WAS pointed out by Barenberg [1] that the physicians of the nineteenth century regarded thrombosis of the renal veins as a common occurrence in young infants. For several decades of the present century, however, little attention was paid to this condition. In 1941 Barenberg and his associates reported five cases discovered among 25 autopsies of infants with epidemic diarrhea of the newborn.

1. Barenberg, L. H.; Greenstein, N. M.; Levy, W., and Rosenbluth, S. B.: Renal Thrombosis with Infarction Complicating Diarrhea of the Newborn: Summary of 5 Cases, Am. J. Dis. Child. **62**:362 (Aug.) 1941.

Case No.	Age	Sex, Race	Duration of Illness	Diarrhea or Other Specific Symptoms	Infection	Dehydration	Acidosis	Renal Findings	Urine	N.P.N. or B.U.N. Mg./100 Cc.
				Group A: Main Renal Vein and Intrarenal Vein Thrombosis						
22	2 wk.	F, W	5 wk.	Diarrhea (bloody) of 6 days' duration	Fever	Moderate	No	Large mass bilaterally palpable early, which decreased in size terminally	Gross hematuria; 2 + albumin	184 to 228 (N.P.N.)
23	4 days	F, W	25 days	Mass on left side of abdomen discovered at 2 days of age	Postoperative wound infection with Staph. aureus	None	Yes; terminal	Mass on left side thought to be kidney and confirmed in operating room	*p*H 7; sp. gr. 1,012; grossly bloody 6 days postoperatively; trace albumin and trace sugar	16.6 (B.U.N.) early
24	2 days	F, N	15 days	Diarrhea of 2 days' duration	Pemphigus neonatorum; Kahn reaction positive, 1:5	Moderate	Yes	No masses palpable	1 + sugar; rest normal	None
25	6 mo.	F, W	8 days	Diarrhea of 2 days' duration	U.R.I. of 7 days' duration; bronchopneumonia; H. influenzae meningitis	Mild	No	In extremis	Postmortem: numerous R.B.C., 20 to 25 W.B.C., 4 + albumin	None
26	8 days	F, N	5 days	Loose yellow stool on admission examination	Difficult breathing and cold of 3 days' duration	Marked	Yes	None	None	None
				Group B: Thrombosis Limited to Intrarenal Veins						
27	9 days	F, W	1 day	Cyanosis of 3 hr. duration	None	None	No	Left kidney palpable	None	None
28	3 mo.	F, W	19 days	Cold of 3 days' duration	Bronchopneumonia; bilateral otitis media	None	No	None	Acid; 3 + albumin; sugar 0; no cells or casts	None
29	6 mo.	M, W	23 days	Jaundice with hematuria of 18 days' duration	Fever of 2 days' duration and convulsions	Moderate	No	None	2 + albumin; 2 + sugar; granular casts	None
30	5 mo.	M, W	6 days	Foul, watery diarrhea of 4 days' duration	Bronchitis	Moderate	Yes	None	1 + albumin; 1 + acetone; granular hyaline casts; occasional W.B.C.	....
31	3 wk.	M, W	4½ wk.	Diarrhea of 3 days' duration	Staphylococcic pneumonia on right	None	None	None	Negative except 1 + sugar	None
				Group C: Thrombosis Limited to Main Renal Vein						
32	4½ mo.	F, W	12 days	Diarrhea for 6 days prior to admission	Bilateral otitis media; bronchopneumonia	Marked	Yes	Negative	Acid; + 1 sugar; amorphous casts and phosphate crystals	None
33	3 yr.	M, W	14 days; death 5 days postoperatively	Vomiting and diarrhea (blood and mucus in stool) of 7 days' duration	Dysentery; stool culture of paracolon bacilli	Marked	Yes	Mass in left upper quadrant confirmed as retroperitoneal at operation	1 + albumin on 5th postoperative day plus granular casts, crystals and rare R.B.C.	None

* U.R.I. signifies upper respiratory infection; N.P.N., nonprotein nitrogen; B.U.N., blood urea nitrogen.

*Veins Grouped According to Location of Thrombosis**

Right		Left		Other Vascular Lesions	Drugs	Symptoms of Shock	Clinical Diagnoses
Thrombosis	Renal Parenchyma	Thrombosis	Renal Parenchyma				
Main renal vein and small branches with organization and calcification	Shrunken pale kidney; liquefaction necrosis of medulla extending into cortex with fresh cortical hemorrhage and necrosis	Main renal vein and all branches with organization and calcification	Same as right	None	Fluids; phenobarbital	None	Uremia secondary to congenital anomaly of kidney, ureter and bladder
Main renal vein, including all branches	Large kidney with massive hemorrhagic infarction; small arteries thickened	Main renal vein completely sclerosed with old organized, calcified thrombus; recent and old thrombi recanalized, filled all branches	Moderately enlarged, fibrosis, tubular atrophy and old hemorrage	Left adrenal vein thrombosis with complete degeneration and necrosis of left adrenal	Sulfadiazine; penicillin; blood; aureomycin; streptomycin; fluids; plasma	.....	Mass in left flank; bronchopneumonia; peritonitis; wound infection
.....	Not involved	Main renal vein extending into all branches	Enlarged kidney with total hemorrhagic infarction	Sagittal sinus lateral sinus thrombosis	Sulfadiazine; BAL	None	Epidermolysis bullosa
Main renal vein extending into small branches	Congestion and hemorrhage in medulla with spotty hemorrhage in lower pole of cortex and early spotty necrobiosis	Main renal vein extending into all branches	Same as right (see fig. 8)	Hyaline thrombi in adrenal capillaries	Sulfadiazine; fluids	Admitted in shock with temperature of 108 F.	Bronchopneumonia; H. influenzae meningitis; brain atrophy
Main renal vein extending into small branches	Hemorrhagic infarct of lower ⅗ of kidney	Interlobar and arcuate veins	Patchy necrosis in cortex and medulla	None	Sulfadiazine; plasma; fluids	.....	Severe malnutrition and dehydration
Arcuate veins	Total hemorrhagic infarction	Arcuate veins	Total hemorrhagic infarction	None	Oxygen; nikethamide, supportive	Terminal	? congenital heart disease
Gross pelvic (intrarenal) veins	Focal medullary hemorrhage	Gross pelvic (intrarenal) veins	Focal medullary hemorrhage	None	Aspirin; sulfathiazole	Terminal	Bronchopneumonia; otitis media, bilateral
Interlobar, arcuate and interlobular veins in upper pole	Hemorrhagic infarction of upper pole	Same as right	Hemorrhagic infarction of upper pole	Thrombosis of pial veins over left temporal lobe, veins in white matter left parietal lobe; agonal thrombus right occipital sinus	Sulfadiazine; sulfamerazine; blood; no fluids	.....	Erythroblastosis fetalis (old); bronchopneumonia
.....	Moderately enlarged, but not unusual	Interlobar, arcuate, interlobular veins in lower pole	Hemorrhagic infarction of lower pole	Focal liver necrosis; focal adrenal cortical necrosis	Sulfadiazine; fluids; penicillin; aspirin	Terminal vascular collapse	Severe diarrhea, dehydration and acidosis
Multiple, of interlobar, arcuate and interlobular veins	Marked hemorrhage in renal papilla and tubular atrophy in areas of venous thrombosis	.....	Slightly enlarged, but no involvement of parenchyma	Thrombosis of longitudinal and lateral dural sinuses	Sulfadiazine; penicillin; blood; fluids	Terminal dependent edema	Parenteral diarrhea; staphylococcic pneumonia on right; aspiration pneumonia; bilateral otitis media
Main renal vein only	Not involved	.....	.....	Acute localized gangrene of colon secondary to thrombosis of small vessels	Sulfadiazine; plasma; fluids	Terminal; sudden death	Diarrhea and ?; pneumonitis
.....	Congenital aplasia	Main renal vein only	Hypertrophy, hydronephrosis, congestion; small arterial infarct; bulk of parenchyma intact	None	Sulfadiazine; plasma; fluids	Postoperative shock	Dysentery; acidosis; ? intussusception

More recently Morrison reported briefly the summaries of 18 cases.[2] Another series of four cases was reported by Fallon.[3] Her series included a patient in whom the diagnosis of bilateral thrombosis of renal veins was made on clinical grounds and who survived, although at the end of a three month follow-up period the blood urea nitrogen level was still elevated. Campbell and Mathews,[4] and Sandblom [5] each reported what appear to be the only successful cases of surgical removal of the infarcted kidney in infants with unilateral thrombosis of the renal vein.

The causation in the vast majority of cases appears to have a connection with diarrhea and the resultant dehydration, and with debilitating states in general, perhaps because of the assumed slowing of the blood stream. In support of this view one may cite the frequency of primary dural sinus thrombosis in children of the same age group. Some cases have been attributed to asphyxia, with its concomitant vascular congestion and stasis. Infection has been incriminated in several instances. In addition, there are cases in which the manifestations of renal infarction begin abruptly without demonstrable antecedent or accompanying illness, and Sandblom [5] has proposed to classify this rarer type as primary, in contrast to the secondary type corresponding to the older term marasmic thrombosis.

All observers are agreed on the paucity of clinical signs in many cases of "secondary" thrombosis. The diagnosis may be suggested by sudden enlargement of one or both kidneys in combination with abnormal urinary findings and azotemia, especially if bilateral involvement is present. If the patient survives the initial period, the kidneys characteristically decrease in size and hematuria declines, though azotemia persists.

In our material 12 cases of thrombosis of renal veins were encountered. The age of the patients ranged from 3 days to 3 years, all but one patient being infants under 6 months of age and four being newborn infants. Among the primary conditions, diarrhea, usually associated with marked dehydration, loomed largest, being represented eight times. One patient had an acute febrile illness with convulsions and hyperpyrexia. In two patients, both infants under 2 months of age (cases 23 and 27), the onset was apparently sudden and not preceded by any demonstrable illness. In the only one of these infants who survived for several weeks after the onset there was clearing of the urine but progressive azotemia. The case histories of three patients are given in detail because they seem especially interesting.

REPORT OF CASES

CASE 22.—J. B. (table), a 2 week old infant who had been vomiting frequently since birth, was admitted because during the last few days she also had profuse diarrhea. On the day of admission, the stools became grossly bloody and large masses were palpable in the region of each kidney. The urine was then grossly bloody. The nonprotein nitrogen level of the blood was 184 mg. per 100 cc. Edema developed; the hematuria and albuminuria continued; the non-

2. Morrison, J. E.: Renal Venous Thrombosis and Infarction in the Newborn, Arch. Dis. Childhood **20**:192, 1945.

3. Fallon, M. L.: Renal Venous Thrombosis in the Newborn, Arch. Dis. Childhood **24**: 125, 1949.

4. Campbell, M. F., and Mathews, W. F.: Renal Thrombosis in Infancy: Report of 2 Cases in Male Infants Urologically Examined and Cured by Nephrectomy at 13 and 33 Days of Age, J. Pediat. **20**:604, 1942.

5. Sandblom, P.: Renal Thrombosis with Infarction in the Newborn: Two Different Forms, Acta pædiat. **35**:160, 1948.

protein nitrogen rose steadily, but the masses in the kidney region disappeared slowly. At times the child had generalized convulsions. She died three weeks after admission.

The autopsy disclosed organized and partly calcified thrombi in both renal veins and in most of the intrarenal branches of all sizes. The kidneys were shrunken and had an irregular surface. The parenchyma on cut section had a parboiled appearance. Microscopic sections showed a

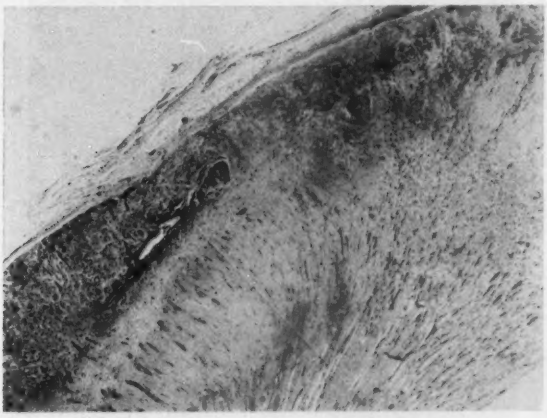

Fig. 1 (case 22).—Low power view of kidney, showing disappearance of renal elements and replacement by fibrosis and necrotic tissue except for a narrow strip of atrophic cortex in the lower part of the field.

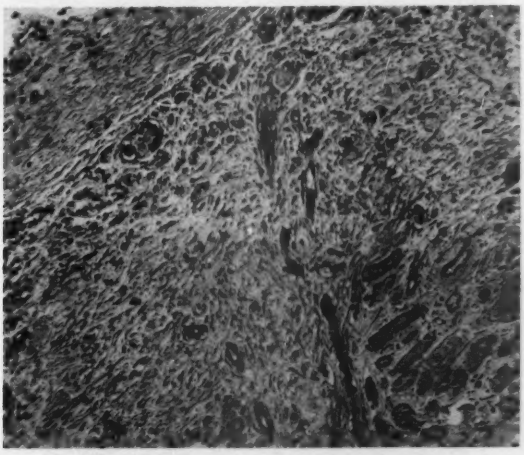

Fig. 2 (case 22).—Area of fibrosis, atrophy and hemosiderin deposits. A group of freshly necrotic tubules is also shown.

picture dominated by fibrosis, with atrophy or total disappearance of all renal elements (fig. 1) and frequent hemosiderin deposits, but there were also areas of fresh necrosis and hemorrhage and a few scattered islands of intact tissue (fig. 2). Old and fresh thrombi were seen in the venous radicles of both kidneys (figs. 3 and 4).

Case 23.—A. P., an infant born normally, had appeared healthy but on routine examination at 3 days of age was found to have a mass in the region of the left kidney. At first there were no urinary abnormalities. An exploratory laparotomy was performed, and the mass was

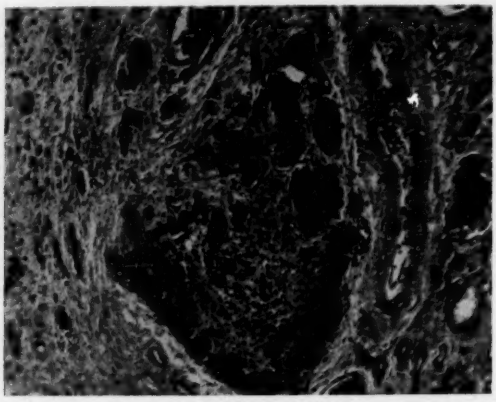

Fig. 3 (case 22).—Calcified, organized thrombus in an intrarenal vein.

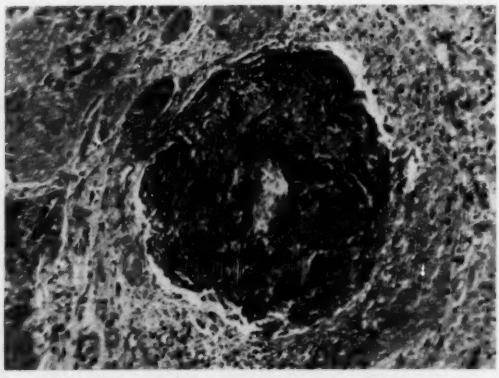

Fig. 4 (case 22).—More recent thrombus in another vein.

Fig. 5 (case 23).—Gross appearance of kidneys, with massive hemorrhage of right kidney, shrunken pale left kidney and transformation of left adrenal gland into necrotic hemorrhagic sac.

identified as kidney, but no biopsy specimen was taken. Subsequently, diarrhea developed, and three weeks after the operation massive hematuria developed. The right kidney became markedly enlarged, and the patient died shortly in shocklike condition.

At autopsy the left kidney (fig. 5) was observed to be shrunken, and the main renal vein, as well as the intrarenal veins at all levels, was occluded by firm, partly calcified organized

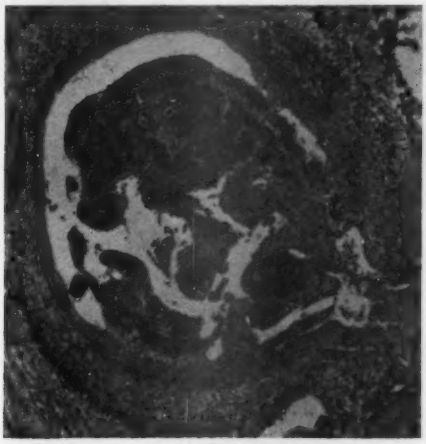

Fig. 6 (case 23).—Recanalized thrombus in large radicle of left renal vein.

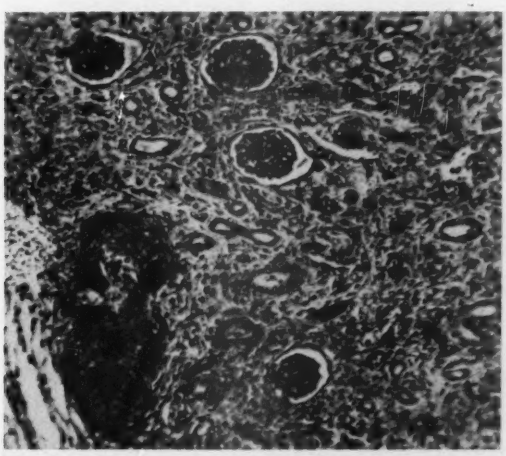

Fig. 7 (case 23).—Left kidney, showing advanced diffuse atrophy of tubules and fibrosis. The right kidney was completely hemorrhagic with recent thrombi in all branches of the right renal vein.

thrombi (fig. 3), some of which showed recanalization (fig. 6). Here and there fresh thrombi were also encountered, and in such areas fresh hemorrhage was present. Elsewhere the parenchyma presented the picture of diffuse atrophy of tubules and glomeruli and fibrosis (fig. 7). The right kidney was greatly enlarged and entirely destroyed by fresh hemorrhage. Fresh antemortem thrombi occluded the small renal veins, as well as the main renal vein. In

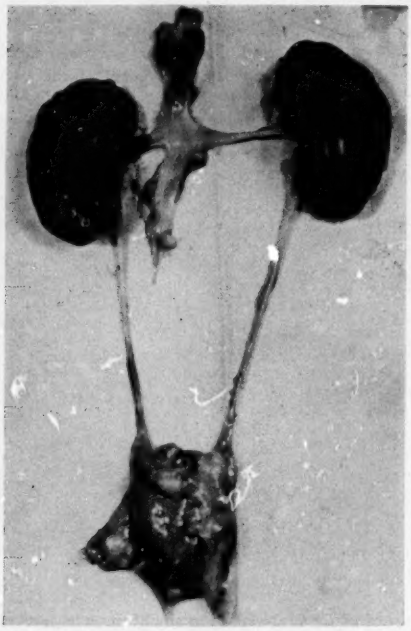

Fig. 8 (case 25).—Complete hemorrhagic infarction of both kidneys.

Fig. 9 (case 27).—Low power view of kidney, showing hemorrhagic infarction with typical streaky hemorrhages extending from medulla into cortex.

this case the obstruction of the venous chanels on the left had evidently taken place early, probably before birth, since at 3 days the kidney was already enlarged, and in such a gradual manner as to produce chiefly atrophy rather than infarction, while the right renal vein became suddenly and completely obstructed three weeks later, producing massive infarction and total renal insufficiency.

Case 27.—The history of a third patient was brief. This 9 day old infant, whose birth had been uneventful and who had seemed healthy for the first eight days of his life, suddenly had an attack of cyanosis and was admitted in shocklike condition. The left kidney was thought to be enlarged. The patient died a few hours later. No urine specimens were obtained. At autopsy, in addition to the pulmonary edema and congestion, the outstanding finding was total

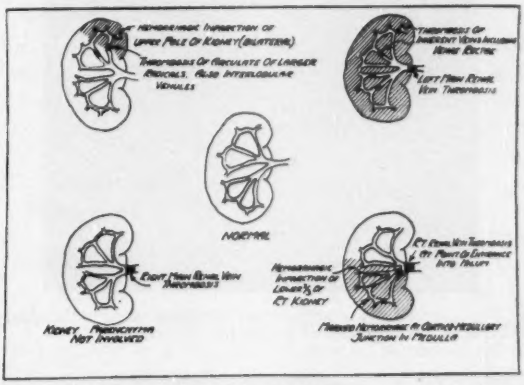

Fig. 10.—Distribution of infarcts in relation to site of thrombosis shown diagrammatically on the basis of actual, representative cases.

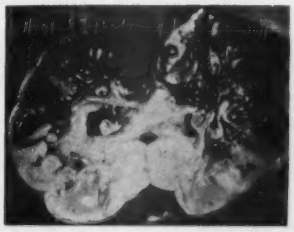

Fig. 11 (case 26).—Photograph of kidney. Note infarction of two thirds of parenchyma.

hemorrhagic infarction of both kidneys (fig. 9). The main renal veins were patent, but recent thrombi occluded the arcuate and interlobular veins.

COMMENT

The 12 cases of thrombosis of renal veins were grouped according to the location of the thrombosis (table). In two cases only the main renal vein was occluded unilaterally. In neither case was there infarction of the kidney. Neither patient had shown clinical signs of renal disease. In five cases the thrombosis affected all branches of the renal vein from the interlobular radicles to the main stem. The process was bilateral in four cases. In all five cases there was hemorrhagic infarction of the affected kidneys, but, in spite of the occlusion of the main stem, there were areas of intact parenchyma of varying sizes. The hemorrhages corres-

ponded in distribution to the thrombosis of the interlobular, arcuate and interlobar veins. The relation of infarction to the involvement of these smaller radicles was also brought out by the observations already referred to in the description of cases 22 and 23, that fibrosis and anemic infarction were seen in areas where the small veins were occluded by old, organized and even ossified thrombi, whereas fresh

Fig. 12 (case 26).—Thrombosis of arcuate and interlobar veins in the absence of infarction. The renal parenchyma in this area showed only patchy necrosis.

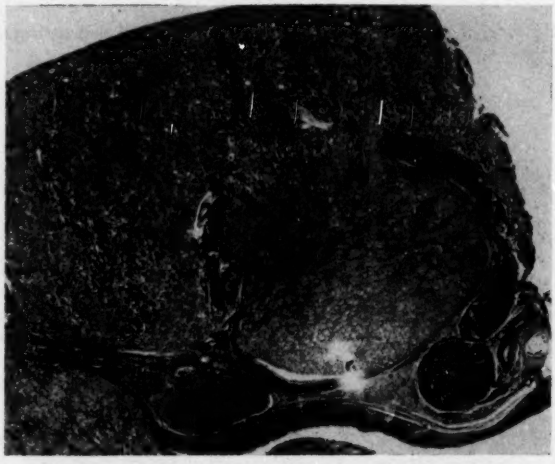

Fig. 13 (case 28).—Thrombosis of main branches and arcuate veins in the absence of hemorrhage.

areas of hemorrhage corresponded in distribution to recent thrombi in the interlobular and arcuate veins.

The observations in the third group of five cases with thrombosis only of the intrarenal branches agree with this interpretation. Here, also, the extent of the infarction was variable and generally less than in the preceding group, and the distribution was dependent on that of the thrombi (figs. 10 and 11).

These observations further suggest that in infancy the thrombosis either is primary in the small radicles and may extend secondarily into the main branches of the renal veins or occurs simultaneously in branches of small and large caliber. No evidence was found in our material which would indicate that retrograde extension of thrombosis from the main stem of the renal vein played a part in the development of the process. Morrison [2] expressed a similar viewpoint.

The dependence of infarction on obstruction of the small veins explains the frequent absence of thrombosis of the main renal vein in the majority of the cases, both in our material and in the cases of Barenberg.[1]

Morrison [2] stressed the fact that thrombosis is not necessarily associated with infarction, while hemorrhage may occur in the absence of even microscopically demonstrable thrombosis. Evidently the rapidity and the degree of the venous occlusion play a significant role. In some of our cases in which extensive hemorrhage had occurred in association with thrombosis of small venous radicles, other veins were filled with recent thrombi but were not surrounded by hemorrhage. Extensive thrombosis was seen in cases 26 and 28 in the absence of hemorrhage (figs. 12 and 13). In cases 22 and 23 some of the thrombi were surrounded by areas of atrophy, indicating the ultimate fate of renal tissue if thrombosis is not immediately followed by infarction.

The frequent association of renal vein thrombosis with thrombosis in other veins is of interest. In four of the 12 cases thrombosis of one or more of the dural sinuses was observed, and in a fifth case there was thrombosis of the small veins in the wall of the colon, associated with hemorrhage and necrosis of the mucosa (table). These observations suggest that the thrombosis of the renal vessels is the expression of a systemic factor. Whether this factor is related to hemoconcentration, to slowing of the blood stream from other causes or to damage of the endothelium is still uncertain. In no case was there morphological evidence of inflammatory changes or necrosis of the veins.

SUMMARY

Thrombosis of renal and intrarenal veins is of comparatively common occurrence in young infants. It is frequently associated with diarrhea and dehydration, sometimes with infection in distant parts of the body, and rarely occurs in a "primary" form not traceable to any antecedent illness. Ten cases of the "secondary" and two cases of the "primary" type were seen in this department during a 10 year period. Renal vein thrombosis is frequently associated with venous thrombosis elsewhere, notably in the dural sinuses.

The thrombosis appears to originate in the small radicle of the intrarenal branches and the interlobular and arcuate veins and extend toward the larger branches or involve all calibers simultaneously. Hemorrhagic infarction seems to depend on the suddenness and completeness of venous obstruction and corresponds in distribution to that of the thrombi in the small venous radicles.

The clinical picture often fails to indicate renal involvement and depends somewhat on the extent of infarction and on the survival time. On the other hand, a dramatic picture may present itself, characterized by sudden enlargement of the involved kidney, shock, hematuria and azotemia.

VII. DIFFUSE HEMORRHAGIC INFARCTION OF THE KIDNEYS WITHOUT VASCULAR THROMBOSIS

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and
RUBEN KURNETZ, M.D.

IN THE preceding article it was pointed out that thrombosis of the renal veins is not necessarily associated with infarction and, on the other hand, that hemorrhage into the renal parenchyma is not invariably accompanied with thrombosis. Apart from hemorrhage into the renal substance occurring as part of a generalized bleeding tendency such as characterizes leukemia, hemophilia or purpura, massive hemorrhage in the renal parenchyma is sometimes observed in the absence of visible structural changes in the veins of the kidney. Our observations suggest, however, that the mechanism in these cases bears a close relationship to that of venous thrombosis.

Our case material contains two pertinent instances of massive destruction of kidney substance by hemorrhage, both occurring in young infants. In the first of these, case 34, the patient, a 3 month old girl, had died from pneumococcic meningitis after an illness of two days' duration preceded by diarrhea. The autopsy, apart from the presence of purulent leptomeningitis and otitis media, showed enlargement and diffuse hemorrhagic discoloration of both kidneys. On the cut surface extensive streaky confluent hemorrhages gave a striped appearance to the renal cortices. Microscopic examination showed no frank thrombosis of any of the renal vessels. The veins of interlobular caliber were commonly dilated and congested, however, and occasionally a few strands of fibrin were seen clinging to the intimal surfaces as though the process of thrombosis were about to begin. The maximally dilated interlobular veins were surrounded by extensive hemorrhages paralleling the course of the vessels. The distribution of the hemorrhages was identical with that seen in a number of cases described in the preceding article on thrombosis of the intrarenal veins.

The findings in a second case (case 35) were almost identical as regards the kidneys. This patient was a 17 day old infant, who was admitted in critical, shock-like condition following an illness of six days' duration characterized by swelling of the legs, edema of the abdominal wall and respiratory difficulties. He died within 24 hours and at autopsy was observed to have suppurative osteomyelitis of both femurs, purulent arthritis of the left knee joint and septic thrombosis of the right umbilical artery. The main renal vessels were normal. The kidneys were hemorrhagic throughout. Microscopic examination showed more extensive hemorrhage than in the preceding case, but, in spite of the confluence of the hemorrhages, a radial streaky pattern was still apparent. The arteries and veins appeared intact, but in the latter a delicate network of fibrin often seemed to indicate incipient thrombosis. As in case 34, frank obstruction of the lumens was nowhere demonstrable as yet.

If either of these patients had survived the severe extrarenal infection, impairment of renal function undoubtedly would have occurred in a short time, as the bulk of the renal parenchyma was destroyed by hemorrhage; yet at the time of death thrombosis was not present.

These observations, combined with the fact that thrombosis itself may not be followed by hemorrhage, suggest that the development of both hemorrhage and thrombosis in the infantile kidney depend on the common factor of extreme venous dilatation and stasis. It would appear that hemorrhage by diapedesis may accompany thrombosis from the start or even precede it, and that the functional element of sudden extreme stasis, with or without thrombosis, is the mechanism responsible for the extensive infarction of the kidneys seen in such cases.

SUMMARY

Extensive hemorrhagic destruction of the kidneys may occur in infancy in the absence of generalized bleeding tendency or local obstructive or other structural changes in the renal vessels. The extreme venous dilatation and incipient fibrin deposits suggest that thrombosis is about to occur when the illness of these patients is cut short by death and that hemorrhage and thrombosis depend on the presence of a common factor, probably sudden complete stasis of the venous blood flow within the infantile kidney.

VIII. LOWER NEPHRON NEPHROSIS

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and
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A DISCUSSION of lower nephron nephrosis and presentation of cases is included conveniently in this series of articles although the exact role of vascular factors on its pathogenesis is by no means established. It is generally assumed, however, that circulatory disturbances within the kidney play an important role in the development of the renal lesions.[1]

Lower nephron nephrosis has become familiar in recent years through the studies of Bywaters [2] in England and Lucke [1] in this country, who proposed the name which has come into general usage. Originally described during World War I, the condition was rediscovered during World War II when Bywaters explored the nature of renal symptoms observed in victims of crushing injuries. Lower nephron nephrosis has also been reported following nontraumatic ischemia of muscle, heat stroke, burns, transfusion reactions, malarial hematinuria (blackwater fever), sulfonamide intoxication and poisoning with mushrooms and other vegetable and chemical substances.

The clinical picture of this highly fatal condition [3] is that of rapidly progressive renal insufficiency. The urinary manifestations are likely to begin with the passage of bloody urine containing free hemoglobin pigment and albumin as well as casts. The urine is acid and has a low specific gravity. Oliguria is characteristic and is frequently followed by anuria. Azotemia invariably accompanies the urinary

1. Lucké, B.: Lower Nephron Nephrosis (Renal Lesions of Crush Syndrome, of Burns, Transfusions, and Other Conditions Affecting Lower Segments of Nephrons), Mil. Surgeon **99**:371, 1946.

2. (*a*) Bywaters, E. G. L., and Beall, D.: Crush Injuries with Impairment of Renal Function, Brit. M. J. **1**:427, 1941. (*b*) Bywaters, E. G. L., and Dible, J. H.: Renal Lesion in Traumatic Anuria, J. Path. Bact. **54**:111, 1942.

3. Burch, G. E., and Ray, C. T.: Lower Nephron Syndrome, Ann. Int. Med. **31**:750, 1949.

manifestations. Moderate hypertension is common, even though the initial shock may have produced hypertension earlier. The mortality is said to be about 90 per cent.

The renal lesion is more or less limited to the distal portion of the nephron. The glomeruli and the proximal convoluted tubules remain intact while the distal convoluted tubules and loops of Henle undergo patchy necrosis and degeneration. The lumens of these structures and of the collecting tubules contain casts of heme pigment, and the stroma becomes edematous and may be infiltrated with inflammatory cells.

The pathogenesis of lower nephron nephrosis is still obscure. It is thought that a combination of factors is responsible for the development of the syndrome. Among these factors the presence of circulating heme pigments, myoglobin or hemoglobin derivatives released from destroyed muscle or blood cells, other toxic substances produced by injured tissues, changes in the composition of blood and body fluids, shock and ischemia resulting from circulatory disturbance within the kidney have received particular attention.[2a]

Lesions corresponding to those described in lower nephron nephrosis were encountered in five cases in the autopsy material studied by us. The patients ranged in age from 2 weeks to 30 months. In contrast to the paucity of clinical manifestations of renal disease in the cases of cortical necrosis described in the first paper of this series, evidence of disturbances in kidney function was plentiful in this group. Renal disease was suspected on clinical grounds in every case, though an accurate diagnosis was not reached, largely because lower nephron nephrosis has not been familiar to the pediatrician.

The primary illness was fulminating hemolytic anemia in one case (case 36), acute cystitis with fever and convulsions in another (case 37). In this case gangrene of a lower extremity developed while the patient was under treatment but after the renal manifestations had become apparent. In the remaining three cases diarrhea with or without vomiting was the leading symptom and in two of these was accompanied with severe dehydration.

No history of poisoning could be elicited in any of the five cases, even though the parents were carefully and specifically questioned. Only three of the patients had received sulfadiazine in customary dosages, and always after renal manifestations were already apparent. The duration of manifestations attributable to renal disease ranged from one to 14 days. In one instance (case 36) grossly bloody urine was found. The patient died before further studies could be made. In the remaining four patients marked albuminuria and marked acidity of the urine were noted, and in three of these the urine had a fixed low specific gravity. Three patients exhibited oliguria and anuria. In the four patients who could be studied for a sufficient length of time significant increases in the blood urea nitrogen level were demonstrable. Edema was noted in only two children. An elevation of the blood pressure was recorded in the oldest patient of the group (case 37).

REPORT OF CASES

CASE 36.—S. K., a 2 week old white boy, was admitted because of icterus and passage of dark red urine. He had been pale since birth but had done well otherwise, had gained weight and had given no concern to the staff of the nursery or the attending physician. The alarming symptoms had begun abruptly on the eleventh day of life.

The examination disclosed icterus, splenomegaly and hepatomegaly. There was evidence of air hunger. The patient was very lethargic. The urine was dark reddish brown and gave a strongly positive reaction with benzidine in the absence of erythrocytes from the sediment. The white blood cell count was 40,000 per cubic millimeter. The hemoglobin concentration of the blood was 7.0 Gm. per 100 cc. and spherocytosis was apparent in stained films.

Results of serologic studies are shown in the following tabulation:

	Blood Group	Rh type
Mother	A_1B	Rh_1 (CDe/e) presumptively heterozygous
Father	A_1	rh (ede/e) .....
Infant	A_1B	Rh_1 (CDe/e) heterozygous

The patient was the product of the mother's first pregnancy. Repeated testing of maternal serum against infant's cells, father's red cells and tests against a variety of Rh-positive and Rh-negative M and N erythrocytes at this time and during two subsequent pregnancies failed to demonstrate antibodies. The mother later had two normal healthy children. Thus in spite

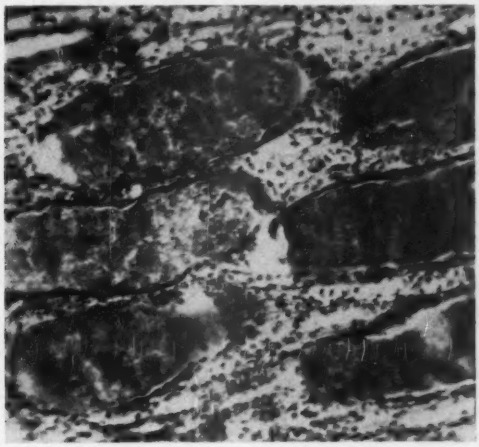

Fig. 1 (case 36).—Heme casts in collecting tubules of medulla.

of the strongly suggestive clinical picture in the patient, erythroblastosis could not be proved on serologic grounds. There was no doubt about the hemolytic, fulminating character of the anemia, however.

The patient received a transfusion of 100 cc. of washed erythrocytes and was placed in an oxygen tent. Convulsions and cyanosis developed, and he died in a shocklike state nine hours after admission.

The autopsy showed splenomegaly, hepatomegaly, multiple focal pulmonary hemorrhages and fairly extensive subdural hemorrhage. Microscopically hemosiderosis and marked erythrophagocytosis were apparent in liver and spleen. The kidneys were grossly enlarged. The renal papillae were diffusely discolored, dark reddish green. The histological picture was one of severe tubular degeneration affecting particularly the distal segments of the nephron, often progressing to necrosis. The lumens of the distal convoluted tubules, collecting tubules and papillary ducts were distended with heme casts (fig. 1).

Comment.—While the cause of this fulminating hemolytic anemia could not be established, it is clear that it was associated with intravascular hemolysis and hemoglobinuria. The presence of the latter symptom prior to transfusion indicates

that this was not a case of reaction to mismatched blood. The renal lesion was typical of lower nephron nephrosis and may have contributed to the rapidly fatal course.

CASE 37.—D. P., a 32 month old boy was admitted because of edema, oliguria, abdominal distention and fever of three days' duration. He had been well until 10 days earlier, when he had an episode of diarrhea and vomiting which lasted five days. There was no history of ingestion of drugs or poisons. Physical examination disclosed little beyond the findings complained of in the history. The bladder was catheterized, and 35 cc. of clear, acid urine was obtained. The specific gravity was 1.006 and remained low on subsequent occasions. All urine specimens contained albumin but no red corpuscles and only occasional leukocytes. The blood urea nitrogen was 57.6 mg. per 100 cc. The blood chlorides were normal, but the carbon-dioxide-combining power was markedly lowered. The blood pressure was measured repeatedly and was somewhat elevated, 124/84.

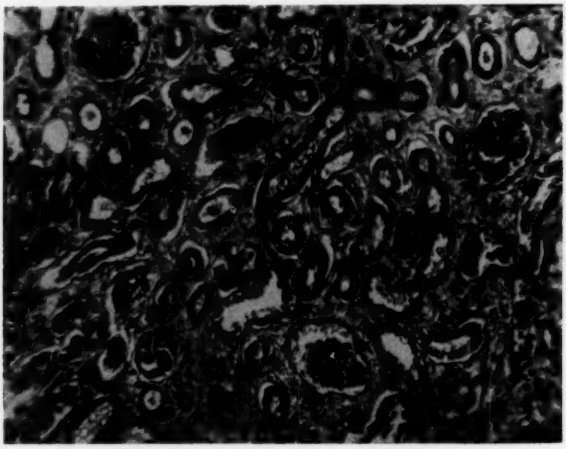

Fig. 2 (case 37).—Tubular necrosis and atrophy affecting chiefly the distal segments and marked interstitial edema.

The oliguria persisted and became virtually complete anuria. Cystoscopy was done without benefit. Abdominal distention, cyanosis, anxiety and restlessness were the outstanding symptoms until death, on the eighth day of the illness.

At the autopsy generalized anasarca, right-sided cardiac dilatation and steatosis of the liver were evident. The kidneys were markedly enlarged, pale and edematous. Microscopic examination showed intact glomeruli and proximal convoluted tubules, widespread necrosis, atrophy and degeneration in the loops of Henle and the distal convoluted tubules and much focal edema of the stroma, as well as occasional infiltrations of inflammatory cells near disintegrating tubules (fig. 2). The collecting tubules and papillary ducts frequently contained masses of eosinophilic granular material resembling heme casts.

Comment.—The clinical picture and the pathological lesions in this case correspond to the classic picture of lower nephron nephrosis, but a clearcut history of antecedent injury, disease or poisoning is lacking. The occurrence of diarrhea and vomiting a few days before the onset of renal manifestations suggests a connection between the two episodes, possibly poisoning as the common basis, an assumption which is likely in view of the patient's age but could not be proved.

The child may have had access to household poisons of which the parents were not aware. In any event, death must be attributed to renal insufficiency resulting from the lower nephron syndrome.

CASE 38.—L. A., an 11 month old infant, granddaughter of a physician, was admitted because of vomiting and diarrhea of three days' duration. She was in a state of severe acidosis and dehydration. The initial urinalysis gave entirely normal results, but on all subsequent occasions the urine contained large amounts of albumin and was strongly acid. The specific gravity, however, continued to range between 1.017 and 1.025. The blood urea nitrogen ranged from 27.5 to 66.5 mg. per 100 cc.

The treatment at first consisted of the usual measures to restore electrolyte and water balance. Sulfadiazine was also given at first but was discontinued shortly. The response to therapy was unsatisfactory. The patient had repeated convulsions, and at one time pulmonary edema, hyperpyrexia and extreme tachycardia developed. At this point she received 0.5 cc. of meralluride injection U. S. P. (mercuhydrin sodium) as well as digitalis preparation and morphine. Two days later anuria developed, and the patient became edematous. The anuria

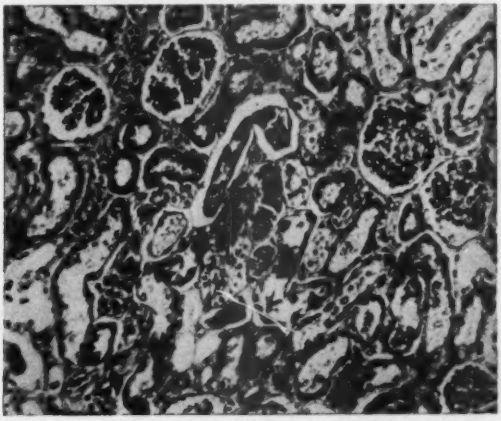

Fig. 3 (case 38).—Patchy tubular necrosis similar to that in figure 2.

persisted for five days, during which time the patient also had carpopedal spasms and lapsed into coma. Thereafter she began to void profusely and seemed improved but died unexpectedly the following day.

The autopsy disclosed severe steatosis and central necrosis of the liver. The kidneys were enlarged, pale yellowish except for the renal papillae which had a dark red brown color. The microscopic picture was similar to that described in the preceding case except for a lower degree of edema of the stroma (fig. 3).

Comment.—Again the clinical and pathological picture of lower nephron nephrosis was seen in the absence of a plausible antecedent illness. Again the possibility of accidental poisoning was considered strongly but could not be proved.

CASE 39.—R. T., a 3 month old Negro boy, was admitted because of convulsions. He had seemed well until a few hours earlier, when he was found beneath the bed covers, pale and not breathing. Artificial respiration had been applied by the fire department.

Physical examination was essentially noncontributory except for convulsions and nystagmus. The urine was strongly acid, had a specific gravity of 1.006 and contained large amounts of albumin and numerous leukocytes. The white blood cell count was 14,600. The blood culture was sterile, and the spinal fluid was normal. The blood urea nitrogen was 20.0 mg. per 100 cc.

The patient was given injections of penicillin and sodium sulfadiazine and magnesium sulfate and received paraldehyde by rectum. Oxygen and external heat were administered. The child remained in coma; at first the extremities were rigid and later flaccid. On the second day swelling and mottling of the left lower extremity was noted in the area where a continuous intravenous infusion had been given. A large area subsequently became discolored and purplish, and multiple bullae developed. The urine continued to contain albumin and leukocytes and soon

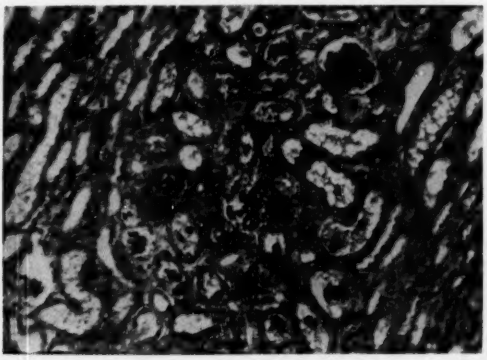

Fig. 4 (case 39).—Extensive tubular necrosis in distal segments. Note intact glomeruli and proximal convoluted tubules.

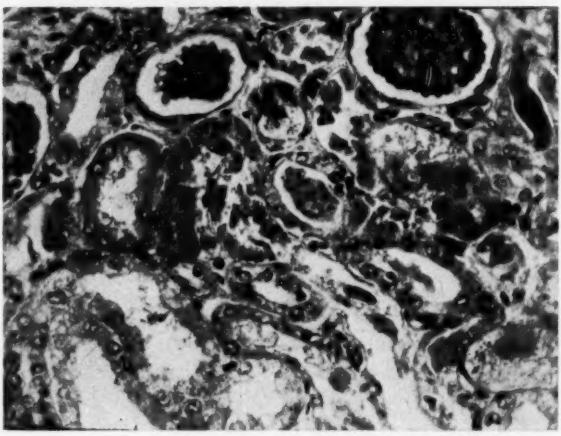

Fig. 5 (case 39).—Higher magnification to show details of tubular necrosis.

became very scanty. The blood urea nitrogen rose to 37.6 mg. per 100 cc. The patient vomited dark brown material and died three days after the onset of his illness.

Post mortem, in addition to early gangrene of the left foot, acute suppurative cystitis, hepatomegaly and marked cerebral edema were the outstanding gross findings. In the region of the left sylvian fissure of the brain there was subarachnoid hemorrhage with hemorrhagic encephalomalacia of the underlying cortex. The kidneys were enlarged to almost twice their normal size and weight. The papillae had a striated dark purple appearance.

Microscopically the picture was that of severe widespread patchy necrosis of the distal portions of the nephrons (figs. 4 and 5). The glomeruli and the proximal convoluted tubules had remained intact. Casts of granular eosinophilic appearance were common in the distal convoluted and collecting tubules of the cortex, but the tubules of the medulla appeared empty. The epithelium of necrotic tubules frequently had sloughed from the basement membrane and formed solid masses in the lumen. There was no evidence of pyelitis or pyelonephritis.

Comment.—The illness of this patient began abruptly with symptoms commonly seen in cases of cystitis or pyelonephritis in infants. The renal lesion was that of lower nephron nephrosis, not of pyelonephritis, however, even though a suppurative cystitis was found at autopsy. Oliguria and azotemia were evident very shortly after the onset of symptoms but 24 hours after a circulatory disturbance of the lower extremity had developed. Possibly this condition contributed in some manner to the renal disturbance. Albuminuria and the passage of acid urine of low specific gravity at the time of admission indicate, however, that the renal parenchyma was already involved prior to the appearance of circulatory changes in the leg and also prior to the use of chemotherapy.

CASE 40.—L. P., a 6 month old infant, had been well until three days before entry, when she began to have profuse watery diarrhea, lapsing rapidly into profound acidosis. On arrival she was critically ill, in profound circulatory collapse, with cold, clammy, mottled skin and flaccid extremities. The urine contained large amounts of albumin. The specific gravity was 1.021 but subsequently ranged between 1.006 and 1.012. The urine was strongly acid and contained a few leukocytes. The blood urea nitrogen was 29.0 mg. per 100 cc. and later, when hydration had been accomplished, rose to 38.8 mg. per 100 cc. The blood chlorides fell from an initial concentration of 100.0 to 72.6 milliequivalents per liter in three days.

The patient was treated in the usual manner for diarrhea and received transfusions of plasma and whole blood without undue reactions. She was also given penicillin and sulfadiazine. She lapsed into coma, the abdomen became distended, fever was persistently present and anuria developed on the seventh day. After two days urine was again passed, but the patient remained in coma and died on the twelfth day after admission.

The autopsy was limited in extent, and consequently the clinical diagnosis of thrombosis of the dural sinus could not be verified. Apart from a terminal aspiration pneumonia, the chief pathological finding consisted in marked enlargement of both kidneys. These organs were soft, flabby and pale except for the dark, congested pyramids. In the right kidney a recent yellow infarct was seen, but the bulk of the renal tissues appeared grossly intact. Microscopically the general picture was similar to that in the preceding case, with marked patchy necrosis and atrophy of tubules and edema of the stroma. The proximal convoluted tubules appeared intact except for general moderate dilatation of the lumens.

COMMENT

The last four cases present a problem in that the cause of the renal lesion is not apparent from the case histories. In two instances the age of the patients and the symptoms suggest accidental poisoning with household poisons, surely a commoner occurrence than is generally realized, but beyond proof in the individual cases. Sulfonamide reactions cannot be incriminated in any of the cases.

The clinical picture of persistent passage of acid urine containing albumin but no red corpuscles, oliguria and anuria, a tendency toward low, fixed specific gravity of the urine and progressive nitrogen retention is similar to that seen in adults.[1] Obviously lower nephron nephrosis must be considered in the differential diagnosis of renal failure in infancy. Further observations are needed to elucidate its mechanism.

SUMMARY

The pathological picture of lower nephron nephrosis was encountered in five patients, among them four infants, who had presented urinary abnormalities, a variable degree of oliguria or anuria and nitrogen retention during life. In one instance the basis of the renal lesions appeared to have been a fulminating hemolytic anemia. In the remainder of the cases accidental poisoning was considered as an etiological factor but could not be proved by history. In several instances diarrhea with acidosis and dehydration may have played a part. The genesis of the renal lesions remain obscure. The syndrome of lower nephron nephrosis must be considered in the differential diagnosis of renal disease in early life.

CONCLUSION

In this series of articles we have presented clinical observations and pathological studies of a large group of cases representing a variety of serious renal disorders in infants. The common denominator of the group is the proved or assumed circulatory origin of the renal lesions. Vascular disturbances of the infantile kidney have received little attention, and most of those described in this series of studies are not even mentioned in current standard texts on pediatrics, evidently because they are regarded as curiosities. Our experience indicates that some of the conditions, notably symmetrical cortical necrosis, renal vein thrombosis, arterial occlusion and lower nephron nephrosis, are not especially rare and deserve more careful clinical study. The etiological basis for these conditions needs elucidation. Our observations indicate that conditions required for the development of the various renal lesions in the infant may differ somewhat from those in the adult and that perhaps the infantile kidney is particularly vulnerable because of differences in the physiology of renal circulation in infancy. These questions can be answered only by physiological and clinical studies, which may also lead to improvements in clinical management and for which the studies reported here can serve only as a starting point.

THALLOTOXICOSIS IN A PRESCHOOL NURSERY

Report of Four Cases

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THE OCCURRENCE of two deaths from an outbreak of thallotoxicosis involving four children who attended the same preschool nursery is herein reported. Although thallium was discovered in 1861 by Crookes,[1] its toxicity was not recognized for some years. Initially thallium acetate was used internally to combat night sweats in tuberculous patients,[2] and later it was employed for the treatment of ringworm infection of the scalp. In 1931 Lubin introduced thallium acetate in a depilatory cream, under the trade name of koremulu. Numerous cases of poisoning were reported from its use. Most poisonings, however, have occurred as a result of the internal use of thallium acetate as a depilatory in the treatment of ringworm in children. Thallium poisonings in industry also have been recorded. In 1920 thallous sulfate was introduced in Germany as a rodenticide under the trade name of zelio. The German literature [3] contains reports of both accidental and homicidal deaths resulting from this product. In 1932 Munch, Ginsberg and Nixon [4] reported the first major outbreak of thallotoxicosis in the United States, in which seven of 20 afflicted persons died. This tragic situation occurred after a sack of thallium-coated barley, intended for use as a rodenticide, had been illegally procured from a warehouse and used in making tortillas. Thallous salts are particularly effective as rodenticides because they are almost without taste or odor.

Although thallium has certain properties similar to those of boron and aluminum,[5] it presents differences which have rendered its correct place in the periodic

From the Department of Pediatrics, University of Texas, Medical Branch, Galveston, Texas.

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classification a matter of speculation. Sometimes it is regarded as an alkaline metal, like potassium or sodium, because of the solubility of its carbonates and hydrates and its inability to precipitate protein. Actually it is closer to lead because it is soft and malleable and has chemical properties, such as its reaction with halogens, similar to those of lead. The atomic weight of thallium is 204, as compared with 207 for lead. Of significance from the toxicological viewpoint, both metals have distinct affinity for nervous tissue.

REPORT OF CASES

CASE 1.—D. N., a 21 month old white girl, was admitted to the Children's Hospital on Oct. 31, 1948 with complaints of bilateral ptosis of the eyelids, ataxia and alopecia. The child had been well until Oct. 22, 1948, when an infection of the upper respiratory tract, characterized by fever (temperature, 100.2 F.), rhinorrhea and cough, developed. The next day her hair began to fall out. These symptoms persisted, and on October 26 the child was observed to have bilateral ptosis. On the following day she exhibited choreiform movements. On two occasions prior to admission the spinal fluid was found to be without abnormality. Physical examination on admission revealed a sleepy, lethargic child who was roused with difficulty but on being awakened was extremely irritable and manifested ataxia and choreiform movements. A diffuse thinning of scalp hair was noted. The palpebral fissures were narrowed, but extraocular movements were intact. Funduscopic examination revealed the disks to be flat and sharply demarcated.

The following were revealed by laboratory studies. The results of spinal fluid examinations made on three separate occasions in the hospital were within normal limits. Repeated urinalyses did not give remarkable results. An eosinophil count of 7 per cent was recorded on one occasion; but otherwise, routine blood studies gave results within the normal range. Kahn and Kolmer tests of the blood elicited negative reactions. Agglutination reactions for typhoid O and H, paratyphoid A and B, Proteus OX_{19}, Brucella and Pasteurella tularensis were all negative. The erythrocyte sedimentation rate was 2 mm. in an hour. Attempts to obtain viruses from nasal washings, whole blood and cerebrospinal fluid were unsuccessful. Chemical study of the urine revealed no evidence of arsenic. Roentgenograms of the long bones disclosed no signs of plumbism. Two weeks after admission (November 13) the presence of thallium in the urine (Reith-Gerritsma method) was reported. Subsequently, the Texas State Department of Health, employing spectrographic technics, confirmed the presence of thallium in a specimen of laked urine.

Shortly after admission to the hospital, the diagnostic possibility of heavy metal poisoning led to therapeutic trial with dimercaprol (BAL), 2.5 mg. per kilogram for each of 12 doses being administered. Marked lethargy, irritability, ptosis and ataxia persisted for a period of 10 days. Subsequently, irritability and lethargy were less evident but alopecia became complete. During the following two weeks there was a gradual diminution in the ataxia to the extent that the patient could stand unassisted. In view of continuing improvement, she was discharged from the hospital November 25.

CASE 2.—L. N., a 28 month old white boy, was admitted to the Children's Hospital on Nov. 1, 1948 with the complaint of sudden alopecia. The child had been well until Oct. 4, 1948, when an infection of the upper respiratory tract, characterized by fever, rhinorrhea, coughing and vomiting, developed. The patient's pharynx and tonsils were injected, and for this reason he was given penicillin on four consecutive days. By October 14 he had fully recovered and returned to nursery school. However, on October 24 coryza and sore throat as well as conjunctivitis and ptosis of the left eyelid developed. On this occasion the patient was given sulfadiazine. Both ptosis and upper respiratory tract symptoms improved, and the child seemed well until October 31, when his hair began falling out with startling rapidity. On admission physical examination revealed an alert white boy of approximately the stated age. An area of alopecia measuring 8 by 16 cm. was noted over the occiput. The eyes, ears and nose were normal. The anterior tonsillar pillars were hyperemic, and the tonsils were mildly hypertrophied. Bilateral cervical lymphadenitis was present; the neck was supple. The lungs were clear to percussion and auscultation, and no cardiac abnormalities were manifest. The abdomen was soft to palpation. The back, extremities and genitalia were not remarkable. Neurological examination disclosed no abnormalities.

On three occasions examination of the spinal fluid revealed it to be normal. Routine blood count and urinalysis gave negative results. Agglutination reactions for typhoid O and H, paratyphoid A and B, Proteus OX_{19}, and Brucella were negative. Attempts to isolate viruses from the cerebrospinal fluid, whole blood and nasal washings were unsuccessful. Examination of the urine by the Reith-Gerritsma method revealed no evidence of thallium. Roentgenograms of the long bones were not remarkable. A chest roentgenogram was interpreted as showing interstitial thickening at the base of the right lung. The alopecia progressed within 10 days to complete baldness; otherwise, the course in the hospital was essentially uneventful. The patient was discharged in good condition on November 13.

CASE 3.—T. R., a 24 month old white boy, had been well until Oct. 20, 1948, when ptosis of the left eyelid and an infection of the upper respiratory tract characterized by rhinorrhea, developed. The next day he became markedly ataxic; gross tremors of the upper extremities developed, and he was somewhat lethargic and irritable. The pupils were dilated but reacted normally to light, and the fundi showed no abnormality. The heart, lungs and abdomen were not remarkable. No evidence of meningeal irritation was observed, and superficial reflexes were normal. The Babinski response was that of plantar flexion bilaterally. By October 22 increasing drowsiness and ataxia had developed. The deep reflexes were definitely hyperactive, and ptosis became more marked. The patient was pale but exhibited cyanosis of the lips and nail beds. A hemogram showed a leukocytosis, with 14,100 white cells per cubic millimeter. The results of differential white blood cell counts were within normal limits, with 6 per cent eosinophils. Urinalysis showed albumin (2+), but no red or white blood cells or casts were found. The fasting blood sugar level was 102 mg. per 100 ml. The cerebrospinal fluid was normal. During a lumbar puncture the expiratory phase of respiration became prolonged and was associated with transient cyanosis. The patient was admitted to the hospital in his home community on the third day of illness (October 22), at which time it was noted that his hair was falling out excessively. On October 23 hoarseness as well as both inspiratory and expiratory stridor developed. Pharyngeal paralysis was present, and ptosis had increased. One severe cyanotic episode and repeated periods of apnea occurred. During the ensuing 72 hours the patient became progressively weaker. Moderate stridor was still present, and cyanosis persisted despite the continuous administration of oxygen and tracheal catheterization under direct laryngoscopy. After a vomiting episode on October 26 moist rales were heard over the base of the right lung. Subsequently, tracheotomy was performed and a moderate amount of tenacious mucoid material removed by aspiration. Tonic seizures, with moderate opisthotonos, occurred every two to five minutes, although no clonic seizures were seen. The temperature rose to 102 F., and despite the use of a respirator, the child died at the local hospital. Autopsy was not allowed.

CASE 4.—G. C., a 36 month old white boy, was treated in another city and died there Nov. 6, 1948. However, autopsy material was studied at our hospital. The historical data supplied with the tissue revealed the onset of the child's difficulty to have been Oct. 20, 1948. Ptosis of the eyelids, ataxia, irritability and cyanotic episodes had developed, and he had slept abnormally long periods. Alopecia did not appear until the day of death. Except for minor variations, the symptoms and signs paralleled those of case 3. Histological sections of the lung showed pneumonitis. Spectrographic study of an extract of brain tissue revealed the presence of thallium.

COMMENT

All four children were exposed to a common source of thallium. Dr. Fred Helm and his co-workers from the Texas State Department of Health found in their investigations that one of the children attending the nursery school was the next door neighbor of an exterminator. This child brought a substance to the nursery school which he offered as candy to each of the children. The nursery school instructor described the taste of the substance as similar to a mixture of cereal and sugar. It then was ascertained that exterminators in this community commonly used a mixture of thallous sulfate, cereal and syrup as a rodenticide. From the evidence obtained, each of the children in whom thallotoxicosis developed had eaten all of the substance offered as "candy."

The symptomatology of these children is entirely compatible with subacute thallotoxicosis. Alopecia is the only characteristic finding among numerous manifestations of this type of poisoning. Usually it does not develop until about three weeks after the ingestion of the noxious agent. Until alopecia appears the clinical findings are not definite, although evidences of respiratory tract disease and central nervous system involvement may be present. These children had such symptoms as tremors, ataxia, ptosis of the eyelids and somnolence which in general simulate the clinical picture of encephalitis or even that due to ingestion of heavy metals. It follows, then, that unexplained polyneuritis or encephalitis should call to mind the possibility of thallium poisoning. Although the initial finding of upper respiratory tract infection was prominent in our patients, such gastrointestinal symptoms as nausea, vomiting or diarrhea are more commonly described as early manifestations.

Prior to the onset of alopecia in case 1 the differential diagnosis included incipient poliomyelitis and encephalitis. The rapid fulminating course with respiratory paralysis and death in case 3 led the attending physician to believe the child had bulbar poliomyelitis. Recurring bouts of upper respiratory tract infection were the only symptoms of note in case 2, and it was not until alopecia appeared that thallium poisoning was suspected. The clinical findings in case 4 seemed to be consistent with the diagnosis of encephalitis lethargica, and this diagnosis was held despite negative spinal fluid findings. It was not until the day of death when alopecia occurred that thallium poisoning was suspected.

A final diagnosis can be reached only by spectrographic or chemical examination of blood, urine or tissue extract, including postmortem material.[6] In case 2 depilation was the sole toxic manifestation, a fact which we interpret as evidence of mild poisoning. Since heavy ingestion was not suspected, we were not surprised at the failure to demonstrate the substance in the urine approximately three weeks later.

The treatment of thallotoxicosis is unsatisfactory. Munch[4] suggests the use of sodium iodide as a means of fixing thallium in the body tissues. For subsequent gradual elimination he advocates the daily intravenous administration of 20 ml. of 3 per cent sodium thiosulfate solution. Gettler and Weiss[2] are of the opinion that excretion of thallium can be affected by forcing fluids. In the treatment of one of our children dimercaprol was employed but did not apparently modify the clinical course. In experimentally induced thallotoxicosis Braun and co-workers[7] found dimercaprol to be of no value. It is realized that to achieve maximum benefit from this therapeutic agent in arsenic and mercury poisonings,[8]

6. Heyroth, F. F.: Thallium: A Review and Summary of Medical Literature, supp. 197 to the Public Health Reports, Federal Security Agency, United States Public Health Service, Division of Public Health Methods, Washington, D. C., Supt. of Doc., Government Printing Office, 1947. Reith, J. F., and Gerritsma, J. A., Jr.: Combined Microgravimetric and Titrimetric Microdetermination of Thallium and Toxicological Material, Rec. d. trav. chim. d. Pays-Bas **65**:770, 1946. Gettler and Weiss.[2]

7. Braun, H. A.; Lusky, L. M., and Calvery, H. O.: Efficacy of 2,3-Dimercaptopropanol (BAL) in Therapy of Poisoning by Compounds of Antimony, Bismuth, Chromium, Mercury and Nickel, J. Pharmacol. & Exper. Therap. (supp.) **87**:119, 1946.

8. Eagle, H., and Magnuson, H. J.: Systemic Treatment of 227 Cases of Arsenic Poisoning (Encephalitis, Dermatitis, Blood Dyscrasias, Jaundice and Fever) with 2,3-Dimercaptopropanol (BAL), Am. J. Syph., Gonor. & Ven. Dis. **30**:420, 1946. Longcope, W. T., and Luetscher, J. A., Jr.: Clinical Uses of 2,3-Dimercaptopropanol (BAL): XI. Treatment of Acute Mercury Poisoning by BAL, J. Clin. Investigation **25**:557, 1946.

dimercaprol must be given shortly after the metal has been ingested. A similar requirement might be expected to apply in thallotoxicosis. Over 20 days had elapsed before dimercaprol was given to our 21 month old patient (case 1).

SUMMARY AND CONCLUSIONS

Thallium compounds, particularly thallous sulfate, are widely used and effective rodenticides which are odorless and tasteless. The latter characteristic and the common practice of incorporating thallium salts in highly palatable, sweetened concoctions render them a real threat to small children. Toxic manifestations vary widely but characteristically include alopecia. As early signs, rhinorrhea and conjunctivitis are frequently misinterpreted as indicating upper respiratory tract infection. Evidences of disturbed function of the nervous system such as ptosis of the eyelids, tremors, ataxia, somnolence, convulsions, coma and polyneuritis are often prominent and of severe degree. Spectroscopic or chemical examination of the blood, urine and tissue extracts establishes the diagnosis. In our experience, by application of these technics, presumptive clinical diagnoses were proved in one of two survivors and, at autopsy, in one of two fatalities. The insidious exposure and high mortality in the four cases reported strongly emphasize the dangers of and the need for further control in the use of thallium compounds.

ADDENDUM

After this paper had been prepared two additional cases of thallotoxicosis following ingestion of a rodenticide containing 2.5 per cent thallous sulfate were reported to us in a personal communication from Dr. Bedford H. Berrey, Harlingen, Texas (to be published).

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Q-T_c INTERVAL OF THE ELECTROCARDIOGRAM IN ACUTE RHEUMATIC CARDITIS IN CHILDREN

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THE PRESENCE and duration of acute rheumatic carditis in children is often difficult to determine clinically. Laboratory aids currently used have not given incontrovertible results. In recent years the electrocardiograph has been employed as an objective aid in establishing the diagnosis of acute carditis. Considerable difference of opinion exists concerning the frequency of electrocardiographic changes in acute rheumatic fever. Sokolow [1] reported electrocardiographic changes (excluding Q-T interval abnormalities) in 21 per cent of 700 cases. These changes consisted of (1) conduction defects, such as partial or complete auriculoventricular block; (2) T wave changes, such as inversion of the T wave in leads I, II or IV or diphasic or flat T waves in leads I and IV, and (3) abnormal rhythms.

Recently Taran and Szilagyi [2] have stimulated interest in the importance of the measurement of the duration of electrical systole (Q-T interval) as an aid in the diagnosis and prognosis of acute rheumatic carditis. They concluded that the Q-T_c (Q-T interval corrected for cardiac rate) was significantly prolonged in all cases of acute carditis. They further observed that Q-T_c was a function of the severity of the carditis. These findings were, in general, corroborated by Abrahams in Britain.[3] However, Pokress and Goldberger [4] and, more recently, Epstein and Gardam [5] have been unable to confirm Taran's observations. Epstein and Gardam found that prolongation of the Q-T_c, per se, is not diagnostic of acute rheumatic carditis. They noted that the Q-T_c was 0.41 or more in 38 per cent of electrocardiograms of patients with active carditis. In the same patients during the inactive phase the Q-T_c was elevated in 27 per cent.

In view of these few but conflicting observations, it was thought worth while to present our own studies of the Q-T interval in acute rheumatic carditis.

Our criteria for active carditis were similar to those used by Epstein and Gardam,[5] namely (1) diminished cardiac reserve as manifested by dyspnea

From the Pediatric Service of Dr. Philip Cohen and the Children's Cardiac Clinic of Beth Israel Hospital.

1. Sokolow, M.: Am. J. Med. **5**:365, 1948.
2. Taran, L. M., and Szilagyi, N.: Am. Heart J. **33**:14, 1947.
3. Abrahams, D. G.: Brit. Heart J. **11**:342, 1949.
4. Pokress, M. J., and Goldberger, E.: Am. Heart J. **38**:423, 1949.
5. Epstein, N., and Gardam, J. D.: J. Pediat. **36**:583, 1950.

and orthopnea, (2) changes in heart size, (3) changing or new cardiac murmurs and (4) electrocardiographic abnormalities such as those listed above as reported in Sokolow's studies.

MATERIAL

Fifty-two patients seen in the wards and children's cardiac clinic at Beth Israel Hospital were studied clinically and electrocardiographically. Twenty-five of these were patients with acute rheumatic carditis. Two additional patients showed clinical evidence of rheumatic fever with no demonstrable evidence of carditis. Of the remaining 25 patients, 14 had inactive rheumatic carditis, 4 had congenital heart disease and 7 had possible heart disease. Their ages varied from 3 to 15 years. There was no significant difference in age, sex or valvular lesions in the two groups.

Children having irregular rhythm, paroxysmal tachycardia, auricular fibrillation or obvious clinical signs of electrolytic imbalance were not included. During the time this study was in progress none of the children studied received salicylates, digitalis or mercurials.

METHOD

Electrocardiographic studies were made on all patients. Repeated electrocardiogram tracings (averaging five for each patient) were made on all patients showing evidence of acute rheumatic fever. The Q-T interval was measured in all standard leads and at least one chest lead (CF_1, CF_4, or both). This was done because measurement in only one lead may give inaccurate results owing to the isoelectric period. Since the Q-T interval is a measurement from the beginning of Q to the end of T, then theoretically the longest Q-T interval found is most nearly the correct one. An isoelectric period at the beginning of Q or at the end of T will tend to shorten the Q-T interval. This is especially true of lead II. By measuring all leads we minimized this effect. Since the cycle length varies, it was decided to measure the longest and shortest cycle in each lead, and these were averaged. The Q-T interval was measured from the beginning of the Q wave to the end of the T wave with calipers under a magnifying lens. We followed the method of Taran and Szilagyi. We visited one of them and were given demonstrations of their technic on several occasions. The $Q\text{-}T_c$ was calculated according to the formula of Bazett [6]:

$$Q\text{-}T_c = \frac{\text{Q-T interval in seconds}}{\sqrt{\text{cardiac cycle in seconds}}}$$

The values of $Q\text{-}T_c$ were calculated by means of a slide rule and by using the nomogram devised by Kissin, Schwarzschild and Bakst.[7] All the calculations were done personally by us. In several cases we calculated the $Q\text{-}T_c$ of the same electrocardiogram independently, and the results checked closely.

The value given by Taran and Szilagyi as the upper limit of normal for $Q\text{-}T_c$ in children is 0.405, and that given by Abrahams [3] and Ashman and Hull [8] is 0.422. In this study we felt that by using 0.422 as our upper limit of normal our findings were more in conformity with those of the latter investigators. Our own control series of 25 cases showed the $Q\text{-}T_c$ to be below 0.422 in 23 cases (92 per cent). However, we realize that the number of cases in our own series is too small to justify making such a positive conclusion.

RESULTS

The table lists our findings. It will be noted that the highest $Q\text{-}T_c$ value during an episode of acute carditis was 0.422 or more in 21 (84 per cent) of our cases. It was prolonged beyond 0.405 in 100 per cent of the cases. However, in our control group we found 2 patients (8 per cent) with $Q\text{-}T_c$ readings above 0.422

6. Bazett, H. C.: Heart **7**:353, 1918-1920.

7. Kissin, M.; Schwarzschild, M. M., and Bakst, H.: Am. Heart J. **35**:990, 1948.

8. Ashman, R., and Hull, E.: Essentials of Electrocardiography, ed. 2, New York, The Macmillan Company, 1941.

Q-T_c Interval in Patients with Acute Rheumatic Carditis and Clinical Rheumatic Fever

Case	Patient	Date	Pulse Rate	Q-T_c, Seconds
1	D. A.	8/17/47	111	0.465
		9/ 5/47	71	0.420
		9/18/47	66	0.412
		9/26/47	66	0.442
		10/ 9/47	70	0.442
		10/16/47	80	0.453
2	L. P.	2/24/48	79	0.442
		3/ 5/48	72	0.428
		3/17/48	80	0.415
		3/26/48	77	0.410
		4/ 7/48	88	0.430
		10/14/49	79	0.432
3	D. O.*	5/26/48	74	0.374
		6/ 7/48	79	0.381
		6/22/48	70	0.380
		7/14/48	78	0.385
4	J. H.	7/30/48	84	0.437
		8/ 4/48	90	0.430
		8/11/48	80	0.422
		9/ 1/48	90	0.438
		9/15/48	86	0.430
		2/23/49	96	0.418
5	M. B.	2/ 4/47	96	0.448
		6/25/47	120	0.445
		1/14/48	105	0.426
		3/ 9/48	96	0.429
		6/23/48	102	0.420
		9/15/48	106	0.448
		2/23/49	102	0.433
		6/ 8/49	98	0.457
		12/28/49	103	0.448
		3/ 7/50	97	0.430
6	S. C.	9/22/48	97	0.453
		10/ 1/48	81	0.408
		10/11/48	84	0.412
7	T. S.	11/20/45	125	0.405
		12/ 3/45	125	0.417
		12/10/45	118	0.443
		7/ 2/47	107	0.405
8	F. P.	3/26/47	82	0.395
		4/ 3/47	97	0.428
		4/ 9/47	95	0.417
		4/15/47	98	0.427
		4/23/47	89	0.423
		4/30/47	100	0.426
		6/15/49	103	0.417
9	E. L.	6/13/47	94	0.432
		11/28/48	64	0.387
10	L. G.	7/18/46	89	0.427
		8/19/46	104	0.431
		8/22/46	95	0.431
		9/ 6/46	97	0.422
		9/19/46	84	0.381
11	R. G.	4/ 1/46	74	0.397
		4/15/46	98	0.395
		4/23/46	88	0.402
		6/14/46	108	0.412
		5/ 4/49	90	0.410
12	L. S.	6/18/46	120	0.415
		6/25/46	115	0.418
		7/ 9/46	104	0.398
13	A. J.	6/12/42	104	0.420
		4/12/50	80	0.445
		4/26/50	92	0.432
		5/ 3/50	80	0.427
14	M. R.	5/11/49	69	0.430
		6/ 8/49	71	0.415
		9/ 6/49	67	0.408
		3/ 9/50	90	0.432
		3/29/50	78	0.397
		4/12/50	90	0.400
		5/24/50	70	0.408
15	S. S.	1/31/49	90	0.428
		2/ 7/49	114	0.430
		2/16/49	80	0.420
		3/ 2/49	96	0.443
		12/26/49	59	0.450

Q-T_c Interval in Patients with Acute Rheumatic Carditis and Clinical Rheumatic Fever—Continued

Case	Patient	Date	Pulse Rate	Q-T_c, Seconds
16	J. S.	6/ 8/48	92	0.433
		6/15/48	68	0.436
		7/ 7/48	114	0.443
		7/14/48	107	0.421
		7/21/48	79	0.424
		7/28/48	88	0.443
		9/15/48	120	0.411
17	G. S.	8/30/48	68	0.398
		9/ 8/48	66	0.400
		9/28/48	71	0.398
		10/ 6/48	71	0.435
		10/15/48	84	0.418
		10/20/48	51	0.397
		10/27/48	95	0.421
		1/12/49	75	0.382
18	B. E.	9/26/47	125	0.422
		9/30/47	71	0.424
		9/ 7/49	105	0.413
		5/17/50	108	0.436
19	E. S.	3/18/47	108	0.445
		10/18/47	97	0.415
		5/ 8/48	104	0.417
		10/ 8/49	80	0.428
20	R. S.	5/17/46	102	0.437
		5/27/46	100	0.432
21	F. S.	3/ 7/50	74	0.446
		3/15/50	82	0.428
		3/21/50	90	0.448
		4/18/50	90	0.447
22	J. D.	3/27/50	103	0.410
		4/ 4/50	67	0.402
		4/12/50	80	0.417
		4/17/50	98	0.427
		4/23/50	95	0.424
		4/24/50	100	0.425
		5/10/50	117	0.440
		5/24/50	97	0.406
23	M. B.*	3/27/50	97	0.352
		4/ 4/50	100	0.372
		4/11/50	100	0.387
		4/17/50	97	0.384
		5/10/50	120	0.413
24	H. B.	3/ 8/39	91	0.432
		6/11/41	110	0.444
		3/27/46	104	0.454
		4/25/46	90	0.453
		11/18/46	88	0.443
		9/17/47	84	0.458
		7/14/48	80	0.428
		9/15/48	67	0.406
		1/19/49	70	0.429
		11/16/49	70	0.460
25	L. B.	5/ 3/50	124	0.403
		5/10/50	104	0.386
		5/19/50	102	0.408
		5/29/50	88	0.385
26	S. O.	1/24/50	83	0.420
		3/15/50	86	0.416
		5/10/50	92	0.420
		5/13/50	79	0.403
		5/19/50	70	0.407
		5/29/50	63	0.385
27	L. N.	5/29/50	92	0.448
		6/ 8/50	90	0.422

* Patient with clinical evidence of rheumatic fever and no demonstrable carditis.

and 12 (44 per cent) with values beyond 0.405 (chart 1). Both control patients with Q-T_c of more than 0.422 were children with inactive rheumatic carditis—one with mitral incompetence and the other with mitral and aortic valvular disease.

In the two cases (cases 3 and 23) of acute rheumatic fever without demonstrable carditis the Q-T_c was consistently below the upper limit of normal. None of the Q-T_c values in these two cases were above 0.387.

COMMENT

We found that 84 per cent of our patients with carditis had at least one Q-T_c value beyond 0.422 second (and all values were above 0.405). When this is compared with our control series, in which only 8 per cent had values above 0.422, we feel that prolongation of Q-T_c is a significant finding in the electrocardiographic diagnosis of acute rheumatic carditis in children.

We attempted to evaluate repeated measurements of the Q-T_c in relation to the severity of the carditis. Chart 2 demonstrates that as the carditis improved the Q-T_c diminished toward normal. In five cases of our series we were unable to demonstrate this effect. However, in these the number of electrocardiograms taken in the later course of the carditis may have been insufficient.

In one of our patients (case 1) who died the Q-T_c remained prolonged until death. In the other patient (case 7), who died of pericarditis and cardiac failure, the Q-T_c was 0.405 shortly before death. Recent studies have shown that the Q-T interval is shortened in rheumatic pericarditis.[9]

In two of our cases (cases 5 and 24) the Q-T_c remained elevated for the three years the patients were under observation (chart 3). A short history of each follows.

CASE 24.—H. B. was first admitted to Beth Israel Hospital in April 1938 with a six day history of arthritis of the left knee, abdominal pain and fever. Three weeks prior to admission he had had a sore throat. On physical examination he had a systolic murmur at the apex as well as arthritis of the left hip and knee. A roentgenogram of the chest showed slight enlargement of the left ventricle. Throat culture revealed a hemolytic Streptococcus. The sedimentation rate varied between 75 and 150 mm. an hour. After two weeks of hospitalization a diastolic murmur was noted at the third left interspace and later confirmed by phonocardiogram. The P-R interval was increased to 0.20 second. Q-T_c was 0.470. After three months the sedimentation rate fell gradually to 10 mm. an hour and a diastolic murmur of aortic incompetence was still heard. He was discharged and followed in the children's cardiac clinic at about monthly intervals. Clinically he appeared well. The sedimentation rate varied from 4 to 25 mm. an hour. Electrocardiograms showed a prolonged Q-T_c and occasionally a P-R interval of 0.20. As time went on, fluoroscopy showed progressive enlargement of all chambers of the heart. In October 1941 he was admitted to Irvington House, where he had a recurrence of fever, arthritis and carditis, with an elevation of sedimentation rate and white blood cell count and an antistreptolysin titer rise from 80 to 200 units. He was discharged in January 1942, and the disease was thought to be inactive. He continued his monthly visits to the Beth Israel cardiac clinic. In January 1944 he had another recurrence of arthritis and was treated with bed rest at home for seven weeks. In 1946 he had a fourth episode of arthritis and was in bed for the next two months. Since then he has visited the cardiac clinic at monthly intervals while being treated with bed rest at home. The sedimentation rate varies from 11 to 57 mm. an hour. Q-T_c remains elevated. He has had no fever or joint pains or other complaints. His pulse rate varies from 72 to 100. Cardiac enlargement has been progressive, and he now has murmurs of mitral incompetence, mitral stenosis and aortic insufficiency.

CASE 5.—M. B. contracted scarlet fever at the age of 4 years, in December 1940. About four weeks later a systolic murmur and tachycardia were noted by his family physician. He was first seen by us in March 1941 in the pediatric clinic at Beth Israel Hospital. At this examination systolic and presystolic apical murmurs were heard. Tachycardia was present. The sedimentation rate was 25 mm. an hour. The child was referred to and followed in the children's cardiac clinic. In June 1941 he was hospitalized for two weeks because of sore throat and fever, at which time double mitral murmurs were heard. The sedimentation rate was 65 mm. an hour. An electrocardiogram showed that there was no definite abnormality. The fever subsided, and

9. Taran, L. M., and Ordorico, D.: Pediatrics **5**:947, 1950.

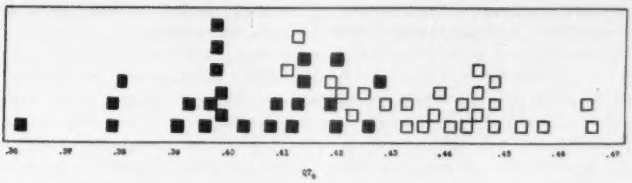

Chart 1.—Highest Q-T_c in carditis cases as compared with control cases; solid blocks represent control cases; white blocks, patients with carditis.

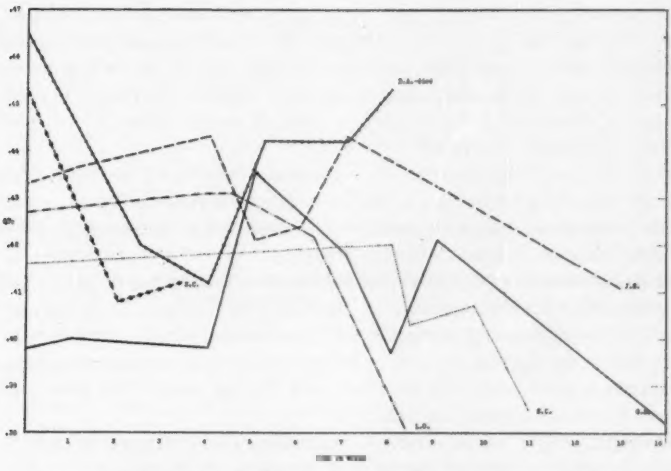

Chart 2.—Q-T_c values during the progress of acute rheumatic carditis.

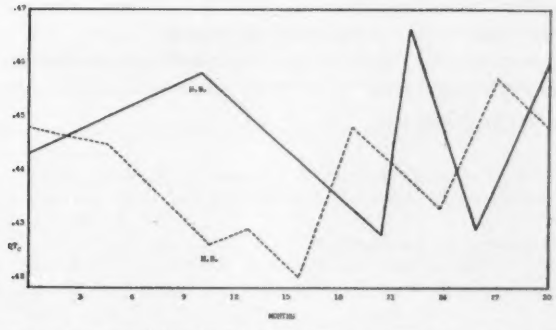

Chart 3.—Prolonged elevation of Q-T_c in two cases of rheumatic carditis.

the sedimentation rate dropped to 13 mm. an hour. He was then followed in the cardiac clinic and kept on limited activity. He was admitted subsequently on three occasions for acute illnesses (1941, for tonsillitis; 1942, for sinusitis; 1944, for aphthous stomatitis).

In April 1945 he had a recurrence of rheumatic fever with arthritis and carditis and was treated in bed at home for four months. After this illness aortic systolic and diastolic murmurs were heard in addition to the double mitral murmurs. He was admitted to St. Francis Sanatorium in August 1945 and remained well there until his discharge in July 1946, with a diagnosis of mitral insufficiency and stenosis. In December 1946 he had an episode of sore throat and fever which was treated with penicillin. After this he was noted to have a reappearance of the aortic murmurs. The sedimentation rate was 10 mm. an hour and the Q-T_c was 0.450. Since then he has been followed at fortnightly intervals. He has been afebrile and asymptomatic. The sedimentation rate has not been elevated. The pulse rate has varied from 84 to 112. However, the Q-T_c has remained elevated, as seen in chart 3.

Both of these cases show clinical evidence of carditis, as manifested by changing heart murmurs. We believe that these cases represent prolonged low grade activity and that the Q-T_c is of particular importance as confirmatory evidence of prolonged activity, especially since in one case, M. B., the sedimentation rate remained normal and in the other it was only slightly elevated. Similarly, the Q-T_c was of prognostic value in our two cases of clinical rheumatic fever with no auscultatory evidence of carditis.

The Q-T_c has been reported as occasionally prolonged in cases of inactive rheumatic fever.[3] Whether this is due to structural changes in the myocardium as a result of previous rheumatic carditis or compensatory hypertrophy subsequent to valvular damage is open to further study.

While an elevated Q-T_c is not the sole diagnostic criterion of acute carditis, it is of great importance in diagnosis if it increases from a previously normal value. It is of further value in following a known case of rheumatic carditis since it tends to decrease as the carditis recedes. Changes in the Q-T_c in active carditis are in our experience more frequently observed than the sum total of all other previously reported electrocardiogram abnormalities.

Although the Q-T_c is an excellent diagnostic aid, it still must be considered in conjunction with the clinical picture and other laboratory methods.

SUMMARY AND CONCLUSIONS

The Q-T interval of the electrocardiogram was studied in 25 cases of acute rheumatic carditis in children.

The measurement of the Q-T interval is discussed.

The Q-T_c is a valuable adjunct in the electrocardiographic diagnosis and prognosis of acute rheumatic carditis in children.

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ELECTROCARDIOGRAMS WITH DEEP S WAVES IN ALL THREE STANDARD LEADS

Report of Ten Cases

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THERE are two types of electrocardiograms in which the main deflection of the QRS complex is directed downward in the three standard leads: those in which prominent Q waves appear in one or more leads, owing to myocardial infarction or severe myocardial damage, and those in which only prominent S waves appear, associated with right ventricular dilatation or hypertrophy, owing to pulmonary disease or other causes. It is the purpose of this study to examine the prominent S wave pattern found in nine cases of congenital heart disease and one of chronic pulmonary disease.

HISTORICAL REVIEW

Burstein and Ellenbogen[1] found nine cases of the two types of pattern in a series of 15,000 electrocardiograms. In eight of their cases coronary occlusion had occurred, and in six pulmonary disease had been or was present. Marcus and Schwartz[2] have described seven cases of deep S wave pattern in patients with chronic pulmonary disease, six of whom were studied at autopsy and showed right ventricular dilatation or hypertrophy. They believed the pattern was due to rotation of the heart about its longitudinal axis as the right ventricle hypertrophied, combined with rotation of the apex toward the back. They mentioned

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1. Burstein, J., and Ellenbogen, L.: Electrocardiograms in Which the Main Initial Ventricular Deflections Are Directed Downward in the Standard Leads, Am. Heart J. **16**:165, 1938.

2. Schwartz, S. P., and Marcus, H.: Electrocardiogram in Pulmonary Tuberculosis: I. Clinical Significance of Concordant Inverted Initial Ventricular Deflections in Patients with Chronic Pulmonary Tuberculosis, Am. Rev. Tuberc. **46**:35, 1942.

but did not describe two cases of the pattern in patients with congenital heart disease. Goldberger and Schwartz [3] have studied 15 cases of downward directed ventricular complexes; of these, five were associated with disease leading to right ventricular enlargement, such as chronic asthma or pulmonary tuberculosis, and showed the deep S pattern, while 10 were associated with anterior and/or posterior myocardial infarction and showed the prominent Q pattern. They presented the observation that if shift of the long axis of the heart is responsible wholly or in part for the abnormal ventricular pattern in the standard limb leads there is a biphasic, or QR, pattern in the unipolar right arm lead, aV_R. In cases in which there is extensive myocardial damage aV_R shows a positive, or R, deflection.

Studies have been made on the related problem of electrocardiograms in which the S waves are prominent and, although not the main deflection of the QRS complex, represent 25 per cent or more of the R wave. These have been found in normal persons as well as in patients with various forms of heart disease.[4] Fershing and Baker,[5] in studying 52 cases with prominent S waves (S equal to 25 per cent or more of the R wave), found a correlation with pulmonary disease and probable enlargement of the right side of the heart in cases in which the unipolar right arm lead, aV_R, showed a prominent R wave (R greater than Q).

MATERIAL AND METHODS

Nine cases have been collected from among those of children with heart disease who attended the Stanford Children's Cardiac Clinic or who were patients of one of us (A. P.). All these children had electrocardiograms that on one or more occasion showed the main deflection of the QRS complex directed downward in all three standard leads. The electrical axis was derived by the method of Carter, Richter and Greene.[6] Five cases were studied with unipolar limb and precordial leads. In three cases vectorcardiograms were constructed from simultaneously recorded standard limb leads. Four children were studied at autopsy, and

3. Goldberger, E., and Schwartz, S. P.: Electrocardiograms in Which the Main Ventricular Deflections Are Directed Downward in the Standard Leads, Am. Heart J. **29**:62, 1945.

4. (*a*) Ashman, R., and Hidden, E. H.: Rightward Deviation of the Axis of the T Wave as an Index of Myocardial Disease, Ann. Int. Med. **12**:1682, 1939. (*b*) Wilburne, M., and Langendorf, R.: Significance of Electrocardiogram with Prominent S Waves in Leads I, II, and III, J. Lab. & Clin. Med. **28**:303, 1942. (*c*) Gardberg, M., and Ashman, R.: QRS Complex of Electrocardiogram, Arch. Int. Med. **72**:210 (Aug.) 1943.

5. Fershing, J., and Baker, L.: Clinical Analysis of the S Wave Pattern Electrocardiogram, Am. Heart J. **35**:106, 1948.

6. Carter, E. P.; Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, Bull. Johns Hopkins Hosp. **30**:162, 1919.

Summary of Clinical Data

Case	Age, Yr.	Disability	Cyanosis	Severe Cyanotic Attacks	History of Squatting	Murmurs	Blood Pressure	Laboratory Data	Special Procedures	Diagnosis
1	8	Malnourished	0	0	0	Systolic, 3 and 4th right interspaces	104/74	Hgb. 15.7 Gm.; r.b.c. 5,750,000	0	Incomplete rotation, with associated cardiac anomalies
2	2½	Severe	Marked	0	0	Systolic, 2 and 3d left interspaces	102/56	Hgb. 29 Gm.; r.b.c. 9,250,000; het. 79%	0	Complete transposition, with a septal defect
3	11	Severe	Marked	0	+	Systolic, 2d right interspace; diastolic, 4th left interspace	90/30	Hgb. 24 Gm.; r.b.c. 11,400,000; het. 81.5%	Angiograms; heart catheterization; unipolar leads; vectorcardiogram; attempted operation	Transposition of the aorta; pulmonary hypoplasia; aortic insufficiency (possible); (autopsy)
4	9	Slight	0	0	0	Systolic, 1st left interspace	114/78	Hgb. 13.7 Gm.; r.b.c. 5,800,000; het. 43%	Unipolar leads	Right aortic arch and right descending aorta; acyanotic heart disease with tachycardia
5	5	Very slight	On effort	0	0	Diastolic and systolic, 2d left interspace	96/74	Hgb. 14.5 Gm.; r.b.c. 5,010,000	Unipolar leads; heart catheterization; vectorcardiogram	Eisenmenger syndrome; multiple congenital defects (imperforate anus, single large kidney, anomalous biliary system)
6	6	Severe	Marked	+	+	Systolic, 2d left interspace	110/80	Hgb. 18.5 Gm.; r.b.c. 6,360,000; het. 57.5%	Unipolar leads; angiograms; heart catheterization; vectorcardiogram; Blalock anastomosis	Overriding aorta; interauricular septal defect; interventricular septal defect; pulmonary stenosis; mongolism
7	3	Severe	Marked	0	+	Systolic, 1st right interspace and 3d left interspace	104/78	Hgb. 26.7 Gm.; r.b.c. 11,000,000; het. 70.5%	Angiograms; attempted operation	Complete transposition of the great vessels; small interventricular septal defect; (autopsy)
8	1½	Severe	Marked	+	0	Systolic, 4th left interspace	.....	.....	0	Extreme tetralogy of Fallot; absent interauricular septum; mongolism; (autopsy)
9	¾	Severe	Marked	+	0	Systolic, left sternal border	70/30	Hgb. 15.7 Gm.; r.b.c. 5,200,000	Unipolar leads	Transposed aorta; mitral stenosis; interventricular septal defect; cerebral thrombosis; (autopsy)
10	65	Severe	Moderate	0	0	None	145/80	Hgb. 22.5 Gm.; r.b.c. 7,100,000	Unipolar leads; vectorcardiogram	Cor pulmonale

findings are reported. One case of chronic asthma in an adult with probable chronic cor pulmonale is also reported; unipolar limb and precordial leads were taken and a vectorcardiogram constructed. These 10 cases are summarized in the table.

REPORT OF CASES

CASE 1.—Barbara S., a 4½ month old white American girl, was first seen on Jan. 4, 1935 and was followed until 1943. Data are limited, as the patient has been lost sight of and the clinic record misplaced.

Physical Examination.—The patient was a small malnourished child with pale bluish lips, not definitely cyanotic. The pulse rate was 80, and blood pressure was 104/74. The apex impulse was felt in the right side of the chest, and there was a harsh systolic murmur heard over the entire precordium, the upper part of the abdomen and the right side of the back, with a thrill in the third and fourth right interspaces.

Laboratory Data.—The hemoglobin level was 15.7 Gm. per 100 cc. There were 5,750,000 red blood cells per cubic millimeter.

Fluoroscopy and Roentgenography (made on numerous occasions).—The appearance was like that of dextrocardia, the smooth right border of the heart being larger than the left and descending lower. On the left there were three curves: an upper anterior, a middle posterior and a lower anterior, which were thought to represent the root of the aorta, the right auricle and the right ventricle respectively. The lung fields were moderately full.

Electrocardiograms (taken on Dec. 1, 1937 and Dec. 28, 1939, fig. 1).—The electrical axis was —120 degrees, and classic dextrocardia was ruled out, as the P and T waves were upright in all three leads.

Clinical Diagnosis.—A diagnosis of incomplete rotation with associated cardiac anomalies was made.

CASE 2.—Lyndon S., a 2½ year old white Canadian boy, was first seen on May 8, 1947, during a three day consultative study at the Stanford University Hospital, having been admitted with a presumptive diagnosis of Eisenmenger complex.

Past History.—The patient had five normal elder siblings. He was born at term. His mother was aged 37, and the pregnancy had been uncomplicated. Cyanosis and a murmur were noted at birth. The boy was weak, and his development was retarded. There were no convulsions, losses of consciousness or severe dyspneic attacks. A marked hilar dance was found on fluoroscopic examination.

Physical Examination.—The patient was a thin, very cyanotic child with slight clubbing of fingers and toes. The pulse rate was 130, respiration rate 32 and blood pressure, 102/56. The apex impulse was felt 7.5 cm. from the midsternal line in the seventh left interspace (the midclavicular line was 4.5 cm. from the midsternum). There was a very soft systolic murmur heard along the left sternal border, best heard in the second and third interspaces. It was heard at the apex but not transmitted beyond the heart.

Laboratory Data.—The hemoglobin level was 28 Gm. per 100 cc. Red blood cells were 9,250,000 per cubic millimeter; the hematocrit reading was 79 per cent.

Fluoroscopy and Roentgenography.—The heart was slightly enlarged, with extraordinary engorgement of the pulmonary vessels and a marked hilar dance. The pulmonary artery segment was concave. There was widening of the upper mediastinum to the right, and the right ventricle appeared enlarged.

Electrocardiogram (taken on May 9; fig. 1).—The electrical axis was —118 degrees.

Course.—The child was discharged without further study. He is now aged 5½, still very cyanotic and in poor health.

Clinical Diagnosis.—The diagnosis was transposition of the great vessels with an interauricular or interventricular septal defect.

CASE 3.—David R., an 8 year 11 month old white American boy, was seen in the clinic with complaints of cyanosis and weakness noted since the age of 18 months.

Past History.—The patient was born on Feb. 9, 1939 at term of a 29 year old mother who had three normal older living children. One sister, born blue, had died

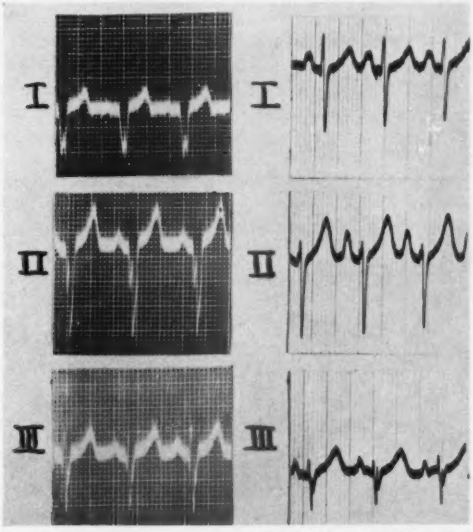

Fig. 1.—Electrocardiograms: left (case 1), taken Dec. 28, 1939; right (case 2), taken May 9, 1947.

at 6 weeks. He was not cyanotic, and early development was normal. At 18 months he had diphtheria and while in the hospital had his first "blue spells." Thereafter he showed some cyanosis every day, gradually increasing until it was present constantly. Clubbing was noted at the age of 3 years, and by 5, at the peak of his disability, he could walk only 10 feet (3 meters) without squatting for relief of dyspnea and cyanosis. From then on his exercise tolerance increased until he could walk a mile (1.6 kilometers) slowly, although from the age of 8 years he sometimes complained of precordial pain on exertion. He never suffered from severe cyanotic or asphyxial spells.

Physical Examination.—He was a thin, swarthy, very cyanotic boy with marked clubbing of fingers and toes. The pulse rate was 80; the respiration rate, 20, and blood pressure approximately 90/30 (hard to obtain). The left side of the chest

was slightly prominent, and the apex impulse was felt in the fourth left interspace just inside the nipple. The left border of the heart was percussed to the anterior axillary line. There was a loud systolic murmur beneath and to the right of the sternum in the second interspace. There was a high-pitched blowing diastolic murmur heard maximally at the left sternal border in the fourth and fifth interspaces. Neither murmur was transmitted well beyond the heart.

Laboratory Data.—In 1948 the hemoglobin level was 24 Gm. per 100 cc.; there were 11,400,000 red blood cells per hundred cubic millimeters, and the hematocrit reading was 81.5 per cent. In 1950, the hematocrit reading was 90 per cent, and there were 13,700,000 red blood cells per cubic millimeter. Arterial oxygen content was 15.13 volumes per cent. The circulation time (arm to tongue with decholin® [dehydrocholic acid]) was eight seconds, and venous pressure was 6 cm. of saline solution.

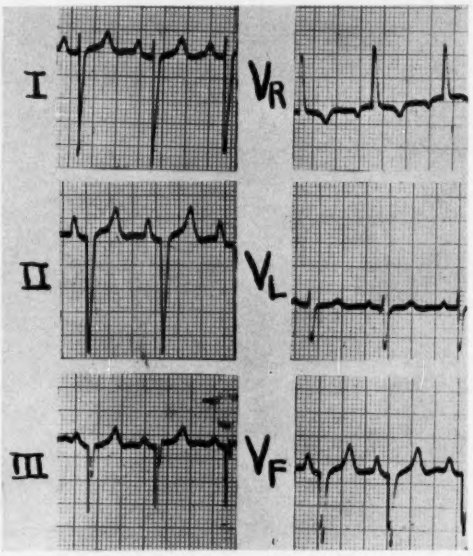

Fig. 2 (case 3).—Electrocardiogram taken Jan. 3, 1950.

Fluoroscopy and Roentgenography.—The heart was enlarged in all chambers. The pulmonic and aortic windows were lucent. The pulmonary markings were accentuated, without hilar dance. The pulmonary artery region was concave, and there was a right-sided aorta.

Angiograms.—Opaque material entered the right ventricle from the right auricle, and most of it left promptly by a markedly overriding aorta. The pulmonary artery ended in a funnel-like narrowing at its bifurcation. With the filling of the pulmonary artery some of the material appeared in the left auricle but did not reach the left ventricle until considerably later. The left ventricle appeared enlarged, and no right to left ventricular shunt was demonstrated.

Catheterization of the Heart (Drs. H. N. Hultgren and H. S. Robertson Jr. on Jan. 4, 1950).—The right ventricular pressure was high. The pulmonary artery could not be penetrated.

Electrocardiograms (fig. 2).—The electrical axis in 1948 was —141 degrees and on Jan. 3, 1950 was —130 degrees. On every examination the main deflection of the QRS complex was a deep S wave. Unipolar limb leads showed a tall R wave in V_R, and the electrocardiographic position was semivertical. In the unipolar precordial leads V_{R3} showed a tiny Q, tall R and inverted T wave; V_1 showed a tiny Q, tall R, absent S, inverted T and peaked P wave; V_2 to V_6 showed a decrease in the amplitude of R and an increase in S from right to left; the P waves were tall and the ST segment slightly elevated in V_3 and V_5. This record was interpreted as showing right ventricular enlargement.

Clinical Diagnosis.—The diagnoses were pulmonary stenosis, with marked overriding persistent right aortic arch, right ventricular hypertrophy, septal defect and abnormal or malplaced incompetent aortic valve cusps.

Course.—The patient's clinical condition became slightly worse, and a mild cerebral vascular thrombosis was suspected from the history. On May 17, he was operated on for pulmonary stenosis and died in cardiac arrest.

Autopsy.—The heart lay transversely, with a large right auricle forming its right border and the whole anterior surface and apex formed by the large right ventricle. The left ventricle lay posteriorly and was much smaller. The aorta was huge and had a persistent right descending arch. The aorta arose entirely from the right ventricle. The aortic valve cusps were deformed and thickened by hard vegetations, but the valve did not appear incompetent. The pulmonary artery also arose from the thick-walled right ventricle. The pulmonary artery was hypoplastic, and its valve cusps also bore a few firm vegetations. The only outlet for the small left ventricle was a large interventricular septal defect.

Pathological Diagnosis.—The diagnoses were transposition of the aorta; right persistent aortic arch and right descending aorta; healed aortic valvulitis, with deformation of the valve; pulmonary artery hypoplasia; healed pulmonic valvulitis; right ventricular hypertrophy and large interventricular septal defect.

CASE 4.—John C., a 9 year old American Negro boy, was first seen on Oct. 3, 1949 during an attack of paroxysmal tachycardia.

Past History.—He was born on March 9, 1940 at term and had two normal older siblings. His development was normal. At the age of 18 months and again at 5 years he was seen at the University of Oklahoma School of Medicine because of vomiting and inability to take solid foods. On both admissions he was found to have a systolic and a diastolic murmur most marked over the pulmonic area. The tentative diagnosis was patent ductus arteriosus accompanied with other congenital cardiac defects. His tuberculin reaction was negative. The early infrequent attacks of vomiting may or may not have been accompanied with tachycardia. At the age of 7 the attacks became more frequent, with the additional symptoms of weakness, dyspnea and "falling down." In the six months preceding admission to the Stanford University Hospital they occurred two or three times a month, and the tachycardia lasted up to three days. Between attacks he was more tired and less active than his brothers, complaining of pains in his legs, but there was no edema or fever.

Physical Examination.—The patient was a thin exhausted child, vomiting, sweating and intermittently losing consciousness. Blood pressure was 114/78. Respiration was periodically stertorous. The heart rate varied between 120 and 275.

When it slowed to 120, the sounds were loud, the neck vessels pulsated strongly and there was a harsh systolic murmur, loudest in the first left interspace near the sternum but heard widely over the entire precordium, in the neck vessels, over the whole left lung field and in the epigastrium. When the heart rate increased to 275, which it did at intervals of two to three minutes, the boy began to gasp, the heart sounds became faint, the neck vessels collapsed, the murmur vanished and sometimes loss of consciousness and vomiting completed the cycle. There was no cyanosis, clubbing or edema. A firm spleen edge was felt.

Laboratory Data.—The hemoglobin level was 13.7 Gm. per 100 cc. There were 5,000,000 red blood cells per cubic millimeter, and the hematocrit reading was 43 per cent.

Fluoroscopy and Roentgenography.—There was a right aortic arch and a right descending aorta, with possible diverticulum of the ascending aorta. The heart was

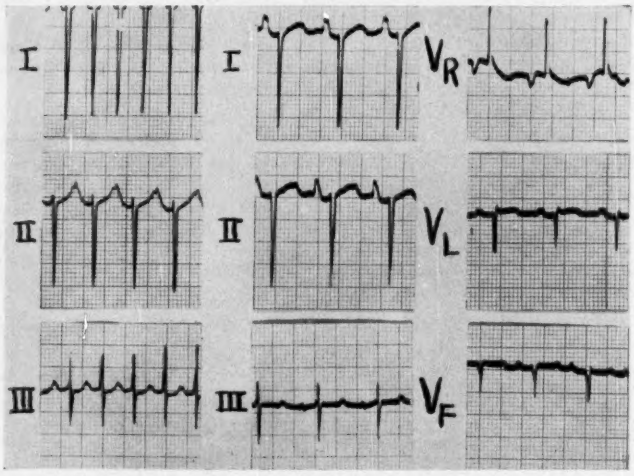

Fig. 3 (case 4).—Electrocardiograms: left, taken Oct. 3, 1949; center and right, taken October 6.

enlarged in both right and left ventricles. (Roentgenograms taken after the cessation of the attack showed decrease in the total heart size, especially in the right ventricular enlargement.) There was a left superior nonpulsating mediastinal shadow, known to have been present four years before, which was thought to be part of the vascular anomalies or, in view of the presence of a large splenic calcification, to represent tuberculous adenitis.

Electrocardiograms.—An electrocardiogram was taken Oct. 3, 1949 during an attack (fig 3). In lead I there was supraventricular tachycardia of 214, increasing to 250, followed by 14 cycles of ventricular tachycardia at 275 and then six seconds of auricular tachycardia with a 2:1 block (auricular rate 250, ventricular rate 125). In leads II, III and IV there was similar activity. The electrical axis was —161 degrees (R exceeded S in lead III). On October 5, there was normal sinus rhythm, with a rate of 110 and an electrical axis of —157 degrees (S nearly equal to R in lead III). On Octber 6, there was a sinus rhythm with a rate of

100 and an electrical axis of —144 degrees (the main deflection of the QRS complex was a deep S in all three leads, fig. 3). The unipolar limb leads showed a tall R in V_R, and the electrocardiographic position of the heart was intermediate. In the unipolar precordial leads V_1 showed an Rs pattern, with deep inverted T and P waves; V_2 showed an rS pattern, with biphasic T waves, and V_3 to V_6 showed an rS pattern, with decreasing tiny R waves, tall peaked P waves and upright notched T waves. The voltage in the unipolar precordial leads was very high, and the record was taken to represent great right ventricular hypertrophy.

Course.—The attack subsided without medication, and the child left California before further studies could be made.

Clinical Diagnosis.—The diagnoses were acyanotic congenital heart disease with paroxysmal tachycardia, right aortic arch and right descending aorta, possible aortic diverticulum, interventricular septal defect and splenic tuberculoma.

CASE 5.—Corky F., a 4 year 9 month old white American boy, was seen in consultation in July 1949. The diagnosis had varied between patent ductus arteriosus and interauricular septal defect.

Past History.—The patient was born in October 1944. On the second day of life he was operated on for imperforate anus. Cyanosis and a murmur were noted at birth, but the cyanosis disappeared in 10 days. Growth and development were normal, but precordial fulness and slight cyanosis on vigorous exercise were noted at 2 years. At 4 years, during a urinary tract infection, roentgenograms showed a single large kidney and gallstones.

Physical Examination.—The patient was a well developed healthy-looking boy with highly colored lips and nails and inconstant cyanosis after effort. The blood pressure before exercise was 98/78 to 70 and after exercise was 110/84. There were dilatation of the veins over the upper anterior part of the chest, slight precordial prominence and considerable enlargement of the left side of the chest. A harsh systolic murmur, maximal in the second left interspace, was heard along the left sternal border, with good transmission to the left upper anterior lung field and axilla and poor transmission to the right side of the chest and epigastrium. It could not be heard in the back. There was an inconstant diastolic murmur (confirmed by a phonocardiogram) at the base of the left lung. The radial and femoral pulses were strong.

Laboratory Data.—The hemoglobin level was 14.5 Gm. per 100 cc. There were 5,010,000 red blood cells per cubic millimeter, and the arterial oxygen saturation was 84 per cent.

Fluoroscopy and Roentgenography.—The cardiothoracic ratio was 60 per cent. The heart was enlarged to both the left and the right, without auricular enlargement, and there were large pulsating pulmonary vessels (hilar dance).

Electrocardiograms (July 22, 1949; fig. 4).—The electrical axis was —125 degrees, and the electrocardiographic position of the heart was intermediate. In the unipolar precordial leads V_1 showed biphasic P waves, absence of S waves, tall R waves and inverted T waves; V_2 to V_6 showed an rS pattern with high voltage and upright P and T waves, and V_5 and V_6 showed a similar pattern with flat notched T waves. The record was taken to represent great right and left ventricular hypertrophy. On March 3, 1950, the electrical axis was —118 degrees.

Catheterization of the Heart (Drs. H. N. Hultgren and H. S. Robertson Jr. on May 23, 1950).—An interventricular septal defect was demonstrated. The pressures in the aorta and the right ventricle were equal. There was no pulmonary stenosis.

Clinical Diagnosis.—The diagnosis was Eisenmenger syndrome, with possible patent ductus arteriosus.

CASE 6.—Gordon W., a 6 year old white American boy with mongolism and cyanotic congenital heart disease, was first seen in July 1948.

Past History.—The boy was born on Feb. 3, 1942 at term of a 41 year old mother who had one normal older living child. The pregnancy was uncomplicated. He was cyanotic from birth, and development was retarded. He had his first severe cyanotic attack at the age of 1 month, with limpness, apnea and syncope; similar attacks, often precipitated by exertion, occurred every three to four weeks during his first year. Thereafter they were less frequent. At the chronological age of 7 he had the mental age of 37 months. He was unable to run and could walk only a block without squatting.

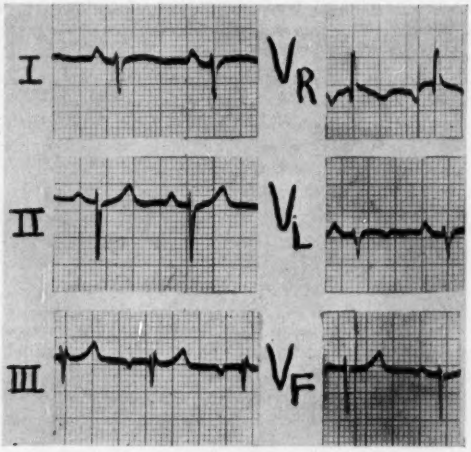

Fig. 4 (case 5).—Electrocardiogram taken July 22, 1949.

Physical Examination.—The patient was a mildly cyanotic child with mongoloid facies and slight clubbing of fingers and toes. The pulse rate was 90, and blood pressure, 110/80. There was slight precordial prominence, with the apex 1 cm. lateral to the nipple in the fifth left interspace. A loud systolic murmur was heard over the entire precordium, maximal and accompanied with a faint thrill in the second and third left interspaces at the sternal border. It was heard in the neck vessels and faintly in the left side of the back. The femoral pulses were palpable.

Laboratory Data.—The hemoglobin level was 18.5 Gm. per 100 cc., red blood cells were 6,360,000 per cubic millimeter; the hematocrit reading was 57.5 per cent, and capillary blood oxygen saturation was 75 per cent.

Fluoroscopy and Roentgenography.—In the anteroposterior view the heart appeared normal, with normal vessels, but in the lateral position it was globular.

Angiograms.—There was simultaneous opacification of both auricles and ventricles. There was a centrally placed aorta suggestive of a truncus arteriosus and a pulmonary artery showing narrowing of its left branch distal to a dilatation.

Catheterization of the Heart (Drs. H. N. Hultgren and H. S. Robertson Jr.).—The presence of a large interauricular septal defect and a large interventricular septal defect (or common ventricle) was proved. The pressure in the ventricle was high. The catheter failed to enter the pulmonary artery.

Electrocardiograms (fig. 5).—The electrical axis was —128 degrees and the electrocardiographic position of the heart was indeterminate. In the unipolar precordial leads V_1 showed an RS pattern (R exceeded S) with upright P and T waves; V_2 to V_6 showed a decrease in R and increase in S from right to left, and V_7 and V_8 showed an rS pattern with decreasing voltage. This record was interpreted as showing right ventricular hypertrophy.

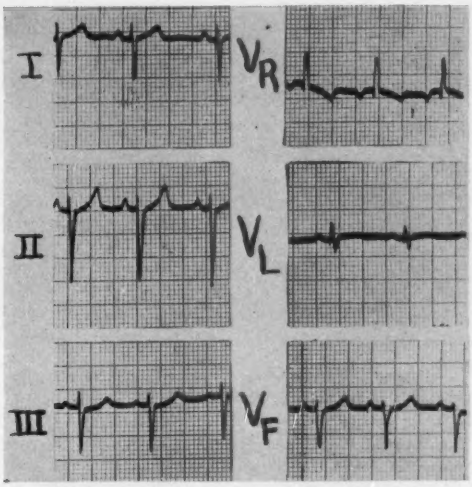

Fig. 5 (case 6).—Electrocardiogram taken May 5, 1949.

Course.—On Jan. 12, 1950 a Blalock operation, using the left subclavian artery, was performed. The child's physical state seemed to be improved by operation, but no improvement in blood oxygen saturation could be shown.

Clinical Diagnosis.—The diagnoses were atrioventricularis communis, overriding aorta or truncus arteriosus, pulmonary stenosis and mongolism.

CASE 7.—Steven S., a 3½ year old white American boy, was first seen in May 1946, for cyanotic heart disease first noted at 3 months.

Past History.—His mother had had rubella in the third month of pregnancy. He was born on April 26, 1943 at term and had one normal older sibling. Dyspnea on crying and cyanosis were first noted at 3 months. He continued to have dyspnea on exertion but no severe cyanotic attacks, and at the age of 3 years he could walk only half a block without squatting.

Physical Examination.—The patient was a moderately cyanotic boy, dyspneic when erect, with marked clubbing of fingers and toes. The pulse rate was 100; respiration rate 22, and blood pressure, 104/78. The anterior fontanel was open.

There was precordial fulness, and the apex impulse was visible in the sixth left interspace in the anterior axillary line. There was a high-pitched systolic murmur at the right base of the heart which was transmitted to the entire right scapular region. There was another lower-pitched systolic murmur best heard in the third left interspace but well heard over the entire precordium.

Laboratory Data.—The hemoglobin level was 26.7 Gm. per 100 cc.; there were 11,000,000 red blood cells per cubic millimeter, and the hematocrit reading was 70.5 per cent.

Fluoroscopy and Roentgenography (unsatisfactory).—The heart was enlarged, especially to the left, with a big blunt apex. The vessels were relatively small, and

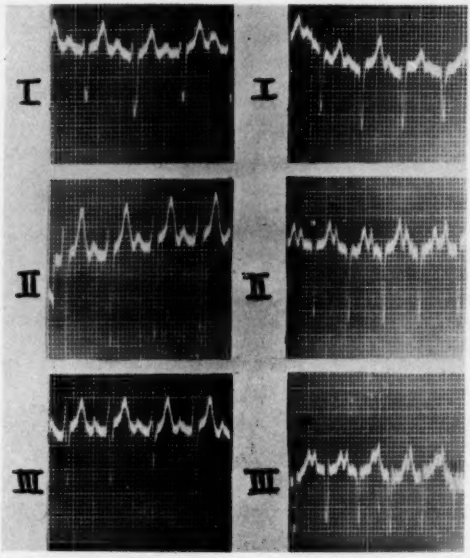

Fig. 6.—Electrocardiograms: left (case 7), taken May 1, 1949; right (case 8), taken April 30, 1946.

the pulmonary artery segment was concave; but the pulmonary artery was visible. The lung fields were hyperemic.

Angiograms (Aug. 8, 1946).—Contrast material passed immediately to the right ventricle, which was moderately enlarged, and almost all of it left promptly by the aorta. A very small vessel was seen that was thought to be a stenosed pulmonary artery. Later roentgenograms showed the contrast material returning from the lungs, but the pathway into the lungs could not be traced. Some material appeared in the left ventricle simultaneously with the filling of the right ventricle, suggesting a right to left shunt. There was no sign of a patent ductus arteriosus.

Electrocardiogram.—An electrocardiogram (fig. 6) was taken May 1, 1946. The electrical axis was —143 degrees.

Clinical Diagnosis.—A diagnosis of tetralogy of Fallot was made.

Course.—The patient died during operation, on September 16.

Autopsy.—The heart was enlarged. There was no anomaly of venous return and no interauricular defect, and the tricuspid and mitral valves were normal. The walls of the right and left ventricles each measured 10 mm. in thickness, but the cavity of the left ventricle was twice as large as that of the right. The aorta arose from the right ventricle, and the pulmonary artery, which was thickened and dilated distal to its normal valve, arose from the left ventricle. Connecting the two circulations was a 1 cm. high interventricular septal defect, the top of which was formed by the edge of the aortic ring. The ductus arteriosus was closed.

Pathological Diagnosis.—The diagnoses were complete transposition of the great vessels, interventricular septal defect, dilated arteriosclerotic pulmonary artery and arteriosclerosis of the pulmonary arterioles.

CASE 8.—Roy M., an 18 month old white American boy with mongolism, was first seen on April 1, 1946, with the complaint of cyanosis since the age of 7 months.

Past History.—His mother had had rubella in the third month of pregnancy. He was born at term. The patient's mental and physical development were retarded. When he was 7 months old his mother noticed that he tired easily, and at this time he began to have dyspneic and cyanotic attacks precipitated by exertion.

Physical Examination.—The patient was a very cyanotic child with mongoloid facies and a disproportionately short fifth digit of each hand. The pulse rate was 132. A loud systolic murmur was heard over the precordium, maximal in the fourth left interspace at the sternal border. It was well transmitted to the lungs and faintly heard in the epigastrium and left side of the back. The radial and femoral pulses were normal. There was congenital dislocation of both hips.

Fluoroscopy and Roentgenography (April 22).—The aorta was normal in size and position, and the pulmonary artery was hypoplastic.

Electrocardiogram.—An electrocardiogram was taken April 30 (fig. 6). The electrical axis was —143 degrees.

Clinical Diagnosis.—The diagnoses made were arterioventricularis communis and mongolism.

Course.—The diagnosis was resented, and the child not seen again until the age of 2½ years, at which time severe cyanotic attacks were occurring every other day. At this time it was thought that he might have tetralogy of Fallot and operation was prepared for, but he died during a cyanotic attack before the operation.

Autopsy (limited to examination of the heart in the gross without removal of tissue, performed at Children's Hospital, San Francisco).—The heart weighed 90 Gm., the right ventricle being larger than the left. The right ventricular wall measured 0.7 cm. in thickness, and the left, 0.8 cm. There was complete absence of the interauricular septum but no anomaly of venous return. There was a 2.2 cm. interventricular septal defect involving both the membranous and the muscular portions of the septum, and some of the chordae tendineae of the mitral valve passing through the defect attached themselves to the papillary muscle of the right ventricle. The pulmonary artery arose from the right ventricle and was hypoplastic, measuring 2 cm. in circumference. The pulmonary valve cusps were thickened, and there was thickening of the endocardium beneath the artery. The aorta was overriding but arose mainly from the right ventricle.

Pathological Diagnosis.—The diagnoses made were absent interauricular septum, extreme tetralogy of Fallot (large interventricular septal defect, extreme dextroposition of the aorta, pulmonary hypoplasia and right ventricular hypertrophy) and mongolism.

CASE 9.—Kenneth T., a 9 month old white American boy, was first seen on July 26, 1949, with the complaint of cyanosis since the second day of life.

Past History.—The patient was born on Oct. 28, 1948 at term of a 25 year old mother who had two normal older children. The pregnancy was complicated by monthly bleeding through the sixth month. His development was normal except for weakness. A systolic murmur maximal along the left sternal border was noted at birth, and was heard until he was 7 months old. Cyanosis, at first intermittent but later constant, was observed from the second day of life. He had cyanotic spells of increasing frequency until at the age of 9 months they occurred daily. Syncope occurred once.

Physical Examination.—The patient was a weak, fretful, gray-cyanotic baby, with marked venous distention of the superficial vessels of the head, face, arms and chest. The pulse rate was 120; respiration rate, 60, and blood pressure, 70/30. The chest showed slight precordial fulness, but the heart was not shown to be greatly

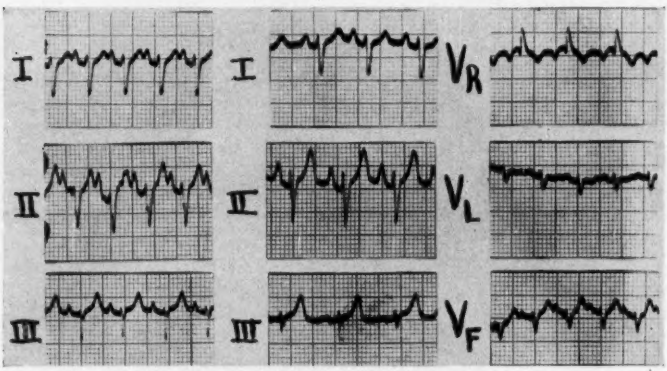

Fig. 7 (case 9).—Electrocardiograms: left, taken July 27, 1949; center and right, taken October 22.

enlarged on percussion. The heart sounds were muffled; the aortic and pulmonic sounds were equally loud.

Laboratory Data.—The hemoglobin level was 15.7 Gm. per 100 cc. The red blood cell count was 5,200,000 per cubic millimeter.

Fluoroscopy and Roentgenography (July 26, 1949).—The heart was enlarged, with a high apex. In the left anterior oblique view there was enlargement of the anterior border of the heart above the level of the right ventricle. The waist of the heart was narrow in the posteroanterior view and the great vessels widened in the oblique and lateral views. The pulmonary artery segment was concave in the posteroanterior view, but the lung vascular markings were full. A diagnosis of transposition of the great vessels was made. Three months later the heart was enlarged, with an elevated apex suggesting an atypical tetralogy of Fallot. The left ventricle in the left anterior oblique view appeared pushed back and up. Another examination a week later revealed hazy shadows in the upper mediastinum suggesting anomalous venous channels.

Electrocardiograms.—An electrocardiogram (fig. 7) was taken July 27, and the electrical axis was —119 degrees. Three months later the electrical axis was —155 degrees, and the electrocardiographic position of the heart was intermediate. In the unipolar precordial leads V_1 showed tall R waves, absence of S waves and inverted T waves; V_2 to V_4 showed an Rs pattern, with biphasic T waves in V_2 and V_3 and upright T waves in V_4; V_5 showed an RS pattern with upright T waves, and V_6, and rS pattern with upright T waves. This was interpreted as representing great right ventricular hypertrophy, the measurements on normal children aged 2 months to 1 year collected by Tudbury and Atkinson[7] being used for reference.

Course.—At 11½ months of age the patient entered the hospital because of increasing cyanosis, dyspnea and weakness associated with an infection of the upper respiratory tract. There were a temperature of 102 F. and two episodes of syncope on the day of entry. Two days later cerebral thrombosis developed, with flaccid paralysis of the left arm, which cleared incompletely during the succeeding days. The patient died during a cyanotic attack three weeks after admission.

Autopsy.—The heart lay transversely in situ and weighed 64 Gm. The right ventricle, the wall of which measured 3 mm. in thickness, accounted for nearly the entire volume of the heart; from it arose both pulmonary artery and aorta. The left ventricle was rudimentary and formed the upper part of the back wall of the heart. It measured 3 cm. from valve to apex with a 2 to 3 mm. thick wall. Behind the posterior mitral valve cusp was a high interventricular septal defect measuring 7 mm. in diameter, so shaped that blood passing from the left ventricle entered the aorta. The mitral valve was thickened and stenotic, measuring 2 cm. in circumference. The left auricle was markedly thickened; its endocardium was thick and contained a few yellowish plaques. Neither pulmonary artery nor aorta was narrowed, but the pulmonary valve was bicuspid, with a rudimentary third cusp. There were a thrombosis of the right middle cerebral artery 2 cm. from its origin and an area of softening in the right parietal lobe.

Pathological Diagnosis.—The diagnoses of transposition of the aorta, bicuspid pulmonary valve, mitral stenosis, with rudimentary left ventricle, high interventricular septal defect and cerebral thrombosis were made.

Case 10.—Charles K., a 65 year old Jewish baker, was first seen when he was admitted to the Stanford University Hospital on July 17, 1947 with complaints of dyspnea and ankle edema of five days' duration.

Past History.—He had had mild asthma for 20 years but was not greatly troubled by it until 1½ years before entry, when his wheezing became worse. Eight months before entry there was an episode of congestive failure necessitating hospitalization. Five days before entry he again became dyspneic, with wheezing respiration, pink frothy sputum and ankle edema.

Physical Examination (made July 17).—The patient was an elderly, barrel-chested, cyanotic, dyspneic man with moderate ankle edema and a liver edge palpable 2 fingerbreadths below the costal margin. The pulse rate was 80; respiration rate, 30, and blood pressure, 145/80. The heart border was obscured by emphysema; there were no murmurs, and the rhythm was regular.

Laboratory Data.—The hemoglobin level was 22.5 Gm. per 100 cc.; there were 7,100,000 red blood cells per cubic millimeter. The urine showed a trace of albumin

7. Tudbury, A., and Atkinson, P.: Normal Values for Standard and Unipolar Leads in Children from Birth to 4 Years of Age; Personal communication to the authors.

with one cast and two to three red blood cells in each high power field. The vital capacity was 2.4 L. Venous pressure was 6 cm. of saline solution. Circulation time (with decholin® [dehydrocholic acid]) was 26 seconds. Skin tests showed no reaction to grains.

Fluoroscopy and Roentgenography (July 19).—The heart was enlarged to both the left and the right, with increased pulmonary vascular markings. A 4 cm.

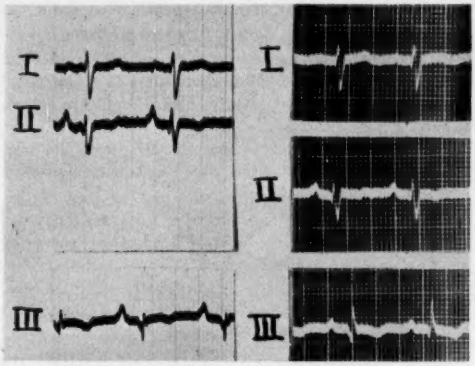

Fig. 8 (case 10).—Electrocardiograms: left, taken July 18, 1947; right, taken December 30.

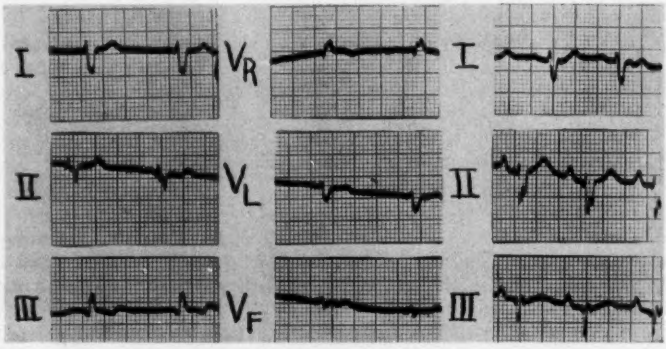

Fig. 9 (case 10).—Electrocardiograms: left and center, taken Dec. 29, 1949, a. m.; right, taken December 29, p. m.

translucent area with a fluid level (which later disappeared) was seen, without surrounding tissue reaction, in the lateral position of the lower lobe of the right lung. The tentative diagnosis was pulmonary congestion with a congenital bronchial cyst or pneumatocele.

Electrocardiograms (taken July 18, fig. 8).—The electrical axis was —145 degrees in its most extreme respiratory variation. Five and a half months later, during his second entry, the electrical axis was —156 degrees, with the main deflec-

tion of the QRS complex directed downward in leads I and II and upward in lead III (not illustrated). Two years later, during his third entry, a morning electrocardiogram showed sinoauricular arrest and a QRS interval of 0.12 seconds' duration in the usual configuration of right bundle branch block (fig. 9). That evening an electrocardiogram showed sinus rhythm with a QRS interval of 0.11 seconds' duration, with the main deflection of the QRS complex directed downward in all three standard limb leads and an electrical axis of —115 degrees.

Course.—He was treated on three occasions in the hospital for episodes of congestive failure. During his third stay he improved briefly, then began to vomit, had a slight fall in blood pressure and became somewhat disoriented and more cyanotic. He died 24 hours later. Permission for autopsy was refused.

Clinical Diagnosis.—A diagnosis of chronic cor pulmonale with congestive failure was made. Death was probably from cerebral infarct.

COMMENT

Clinical.—The common factor in these 10 cases (table) appears to be the presence of one or more cardiac defects or a disease leading to right ventricular dilatation or hypertrophy. This is clear in the four cases in which autopsy was done. In case 3 and case 9 both the pulmonary artery and the aorta arose from the right ventricle. In case 3 there was, in addition, a deformity of the aortic valve and a hypoplastic pulmonary artery, which could only have added to the already terrible load on the right ventricle. In case 7 there was a complete transposition of the great vessels, a severe malformation, with the right ventricle carrying the burden of the systemic circulation. In case 8 there were three malformations, all leading to right ventricular hypertrophy, namely, pulmonary hypoplasia, an overriding aorta and absence of the interauricular septum. It is also clear in two cases in which the diagnosis, although not confirmed by autopsy, was known with a high degree of certainty. In case 6 angiograms showed a large interauricular septal defect, with a pulmonary stenosis and an overriding aorta (or truncus), all affecting the right ventricle. In case 10 it was fairly sure on clinical grounds that chronic asthma had led to cor pulmonale. As noted by Marcus and Schwartz,[2] the appearance of the deep S pattern electrocardiogram in this type of case indicated a bad prognosis.

In the other four cases matters were not so clear. In case 2, with a clinical picture of severe disability, marked cyanosis and polycythemia, there may have been a complete transposition of the great vessels, but the diagnosis was in doubt. In case 4 it is safe to assume that the bouts of tachycardia led to inadequate cardiac output and right ventricular dilatation, although it is not evident why the degree of axis deviation in the electrocardiograms increased slightly after the attack subsided. In connection with case 1, in which incomplete rotation was associated with one or more other cardiac anomalies (presence of murmur), it is known statistically that with incomplete rotation the associ-

ated anomalies are apt to be severe. However, in the absence of cyanosis and polycythemia, we have no evidence that the right ventricle was affected. The solution may be that the bizarre electrocardiogram was due to a shift in the normal position of the heart on a congenital basis rather than as a consequence of right ventricular hypertrophy. One may have to fall back on some such explanation in case 5 in which the catheterization studies led to the diagnosis of an Eisenmenger syndrome, and in which the good physical status, mildness of cyanosis and lack of polycythemia of the patient tended to rule out the presence of a severe malformation.

Electrocardiograms.—In connection with the electrocardiograms a brief review of the method of deriving the electrical axis, or main vector of the QRS complex in the standard three limb leads may be helpful. In figure 10 the large Einthoven triangle has been divided into six areas labeled *A* through *F*. In a normal electrocardiogram the axis falls in area *A*, that is to say, the area in which the main deflection of the QRS complex is positive, or directed upward, in all three leads. When it falls in area *B*, there is right axis deviation, that is, the main deflection is negative, or directed downward, in lead I and positive, or directed upward, in leads II and III. In area *C* there is a severer degree of right axis deviation, with the main deflection negative, or directed downward, in leads I and II and positive, or directed upward, in lead III. In area *D*, past the turning point of —150 degrees, the main deflection of the QRS complex is negative, or directed downward, in all three leads. It is electrocardiograms of this pattern that we have collected here.

Similarly, there is left axis deviation in area *E*, where the main deflection is positive, or directed upward, in leads I and II and negative, or directed downward, in lead III. In area *F* there is a severer degree of left axis deviation, with the main deflection positive, or directed upward, in lead I and negative, or directed downward, in leads II and III.

Considering now the electrocardiograms whose main deflections make the electrical axis fall in area *D*, there are at least three possibilities to be discussed. The first is that this type of electrocardiogram may be produced by alteration in conductivity of the surrounding tissue due to pleural or pericardial effusion. Burstein and Ellenbogen [1] stated the belief that this factor played a role in their series. In the cases presented here there were no signs of effusions, and none were found in the four cases in which autopsy was done. Furthermore, there is good evidence that various tissues conduct equally well;[8] consequently this

8. Kaufman, W., and Johnston, F. D.: Electrical Conductivity of the Tissues near the Heart and Its Bearing on Distribution of Cardiac Action Currents, Am. Heart J. **26**:42, 1943.

factor may largely be ignored in studying electrocardiograms. Effusions appear to decrease the amplitude of the QRS complex rather than to distort its shape.

Second, there is the possibility that this represents an atypical form of right bundle branch block. Right bundle branch block can produce a downward directed main deflection in all three standard leads, as has been shown by Wilson, Johnston and Barker,[9] but in their cases the QRS interval was grossly prolonged, whereas in the electrocardiograms of these children the QRS interval in no case exceeded 0.08 second

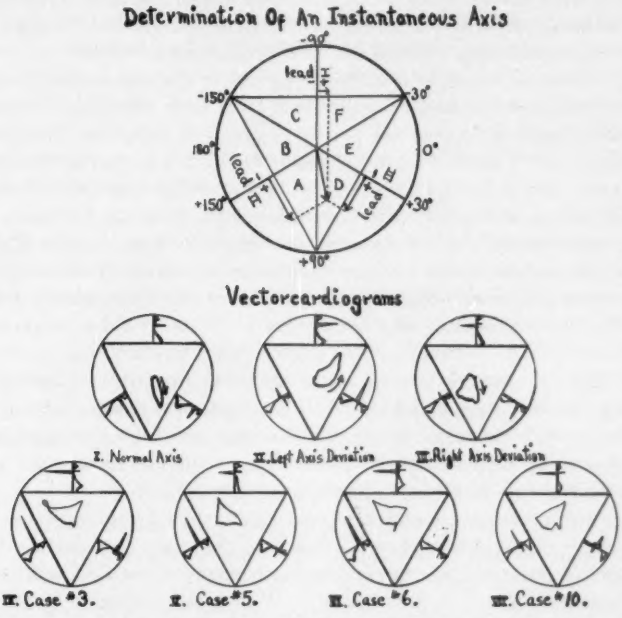

Fig. 10.—Electric axis deviation as related to physical rotation of the heart.

and the precordial leads failed to show right bundle branch block. It is interesting, however, to see how the vectorcardiogram constructed in case 5, of the child with probable Eisenmenger syndrome, with a QRS interval of 0.08 second, resembles the vectorcardiogram of a young man with tetralogy of Fallot, who undoubtedly had a bundle branch block (QRS interval of 0.14 second), in the article just mentioned. In the case of the adult with cor pulmonale due to chronic asthma the pattern

9. Wilson, F. N.; Johnston, F. D., and Barker, P. S.: Electrocardiograms of an Unusual Type of Right Bundle-Branch Block, Am. Heart J. **9**:472, 1934.

appeared without widening of the QRS complex on one occasion two years before death. In its terminal appearance it may have represented atypical bundle branch block, since right bundle branch block in the usual pattern was present 12 hours previously.

Third, there is the idea presented by Goldberger and Schwartz [8] that the pattern is due to rotation of the heart about its three axes in association with enlargement of the right ventricle—that is, clockwise rotation about the long axis of the heart so that the right ventricle lies more anterior and the left more posterior than normally; clockwise rotation (seen from below) about the vertical axis so that the apex is directed back, and rotation about the horizontal coronal axis so that the apex is not only back but up. This is the view to which we subscribe.

Evidence is found for it in the appearance of the unipolar limb leads. In the five cases in which unipolar limb leads were taken and in which bundle branch block was not present, a qR or R deflection was found in lead V_R. This is the pattern that is found in leads taken from the scapular area in normal persons, and one may deduce that the right arm lead in these cases was facing the ventricular wall owing to tipping of the apex, instead of "looking into" the negatively charged cavity of the heart, as it does usually. Owing to the negative charge of the cavity of the ventricles, leads which "look into" this cavity (through the thin-walled auricles) show a negative, or QS, deflection. This is the pattern that appears in V_R and V_L in the vertical heart normally.

That the anatomic position of the apex was directed back and up is known in two cases (cases 3 and 9) from personal observation of the heart in situ at autopsy. In one of these cases, case 9, the apex appeared back and up on fluoroscopic examination; in all the other cases the roentgenograms showed no striking displacement.

Further evidence in favor of unusual rotation being the cause of this type of electrocardiogram is found in the study of vector cardiograms constructed from two simultaneously recorded standard limb leads in four cases (cases 3, 5, 6 and 10). With paper moving at 75 mm. a second the individual waves can be spread out sufficiently in the recording to permit up to 10 or more instantaneous axes or vectors to be measured in sequence throughout the QRS complex. When recorded on the Einthoven triangle, the tips of these instantaneous axes or vectors can be connected to form a loop. This loop is the frontal projection of the actual vectors appearing in three dimensional space during the electrical excitation of the ventricles as the impulse travels down the septum from the auriculoventricular node through the bundle of His and spreads out through the ventricle walls from the apex upward.

Disregarding the various theories of the precise genesis of these instantaneous vectors, their frontal projection, as photographed with

a cathode ray oscilloscope [10] or constructed as we have done from simultaneously recorded standard leads, is normally a fairly narrow loop, such as pictured in figure 10 *I*. This pattern when translated into the three standard leads shows the main deflection of the QRS complex positive, or directed upward, in all three leads. Left ventricular hypertrophy is often associated with a loop such as shown in figure 10 *II*. This loop has its longest dimension in area *E* or *F* of the Einthoven triangle and when translated into the standard three leads has the pattern of left axis deviation. Similarly, right ventricular enlargement frequently results in a loop such as shown in figure 10 *III*, a wide loop running clockwise, as did the normal loop, in contradistinction to the loop of left axis deviation, which runs counterclockwise. It has its longest dimension in area *A* or *B* of the Einthoven triangle and when translated into the three standard leads has the pattern of right axis deviation. A reasonable explanation for the changes in appearance of the loop is found in the changes in heart position, both physical and electrocardiographic, associated with ventricular hypertrophy.

This can easily be visualized if one draws radiuses from the origin of the normal loop to its edges and then places toothpicks of proportional length into the septum of a normally positioned modeled heart so that their frontal projection forms a similar loop. This has been done by Gardberg and Ashman [4c] in their study of the anatomic position of the heart in relation to the electrocardiogram. In the normal heart, the left ventricle is slightly predominant and the instantaneous axes or vectors after the impulse has passed down the septum are directed to this ventricle. The angle of the normally positioned septum is such that the loop runs clockwise in its frontal projection. This basic pattern does not have to be altered in the succeeding manipulations.

If one rotates the model counterclockwise about its long axis so that the left ventricle becomes more anterior than usual and then moves the apex laterally to the left so that the heart lies more horizontally than usual, these being the physical changes associated with left ventricular enlargement, one sees that the frontal projection of the radiuses now forms a loop like that of figure 10 *II*.

If one then rotates the model so that the right ventricle lies more anterior than usual and the left more posterior than usual and moves the apex to the right so that the heart lies more vertical than normally, these being the changes associated with enlargement of the right ventricle, one observes the frontal projection of the tips of the radiuses to form a loop similar to that illustrated in figure 10 *III*.

10. Wilson, F. N., and Johnston, F. D.: Electrocardiogram, Am. Heart J. **16**:14, 1938.

Finally, if to the rotation of the heart associated with right ventricular hypertrophy one adds movement of the apex so that it is directed up and back, one observes the frontal projection of the tips of the radiuses to form a loop similar to those illustrated in figure 10 *IV* to *VII*. These are the vectorcardiograms constructed in four of our cases in which standard leads were recorded simultaneously.

An argument against this approach is that if one starts with a loop in space one can by manipulation turn it into almost any other loop one desires. Furthermore, to obtain the loop similar to those of our four cases, one must move the apex of the modeled heart through a large angle in pushing it back and up. But clearly there is a certain rough relation between the anatomic changes in heart position and the changes in the electrocardiogram, since left axis deviation can be found in healthy stocky persons and in pregnant women, in whom the heart lies horizontal because of a high diaphragm. Similarly, right axis deviation is found in the electrocardiograms of asthenic persons with long narrow vertical hearts. It is curious that the odd form of electrocardiogram we have discussed has been reported only in patients with disease leading to right ventricular hypertrophy, since if the apex of the heart in a person with left ventricular hypertrophy were to move very far anterior and up, and it has a tendency to move anterior during left ventricular hypertrophy, one would obtain an electrocardiogram like the ones of our 10 patients. It may be that the obstruction of the anterior chest wall and the mode of attachment of the great vessels and the pericardium hinder this movement, whereas they may facilitate an opposite movement in patients with right ventricular hypertrophy.

SUMMARY

Ten cases are reported in which there were electrocardiograms with the main deflection of the QRS complex directed downward in all three standard leads. The common factor appeared to be disease leading to right ventricular dilatation or hypertrophy. Reasons are presented for believing that this pattern of electrocardiogram is associated with physical rotation of the heart, with the apex directed back and up, and that it represents an extreme form of right axis deviation.

Dr. David Rytand, Director of the Electrocardiography Laboratory of the Department of Medicine, Stanford University School of Medicine, gave generously of his time and assistance in the course of this study.

METABOLIC STUDIES IN PATIENTS WITH INTOLERANCE TO COMPLEX CARBOHYDRATES

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THE CONCEPT of "carbohydrate intolerance" is ancient and vague. It arose from the clinical observation that in some persons intestinal symptoms, diarrhea and usually steatorrhea, developed when they were fed complex carbohydrates in amounts that were tolerated by most persons. This concept has been commented on regularly in the literature since at least as early as 1868 [1] and was emphasized to American pediatricians by Dr. John Howland in a presidential address before the American Pediatric Society in 1921.[2] It has not been possible to define this condition exactly, nor is it clear whether "celiac disease" and "carbohydrate intolerance" are the same or related conditions. But that it is a real disorder has been readily affirmed by numerous clinicians experienced in dealing with chronic intestinal disorders in infants and children.[3] The literature contains limited quantitative data concerning

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1. Smith, E.: On the Wasting Disease of Infants and Children, London, J. Walton, 1868. Finkelstein, H., and Meyer, L. F.: Über Eiweissmilch, ein Beitrag zum Problem der künstlichen Ernährung, Jahrb. f. Kinderh. **71**:525-570, 1910. Porter, L., and Dunn, C. H.: Some Studies of Sugar in Infant Feeding, Am. J. Dis. Child. **10**:77-85 (Aug.) 1915. Dunn, C.: Some Studies in Fat Indigestion, ibid. **9**:225-232 (March) 1915. Nobécourt, P., and Philippon, H.: Étude d'un cas d'intolérance pour les farines chez un bébé de dix mois, Bull. Soc. de pédiat. de Paris **16**:375-388, 1914.

2. Howland, J.: Prolonged Intolerance to Carbohydrates, Tr. Am. Pediat. Soc. **33**:11-19, 1921.

3. Herter, C. A.: On Infantilism from Chronic Intestinal Infection, Characterized by the Overgrowth and Persistence of Flora of the Nursling Period, New York, The Macmillan Company, 1908. Sauer, L. W.: Celiac Disease (Chronic Intestinal Indigestion): Etiology, Prognosis and Standardization of Treatment, Am. J. Dis. Child. **34**:934-954 (Dec.) 1927. Fanconi, G.: Der intestinale Infantilismus und ähnliche Formen der chronischen Verdauungsstörung, Berlin, S. Karger, 1928. Morse, J. L.: Celiac Disease, New England J. Med. **204**:668-675, 1931. Parsons, L. G.: Celiac Disease: Rachford Memorial Lectures, Am. J. Dis. Child. **43**:1293-1346 (May) 1932. Haas, S. V.: The Value of the Banana in the Treatment of Celiac Disease, ibid. **28**:421-437 (Oct.) 1924.

the defects in absorption and disturbances in metabolism which accompany carbohydrate intolerance [4] and none that we have been able to find correlating these with electrolyte balance. Therefore, it is our intention to present metabolic balance data collected from patients who exhibited such an "intolerance" to complex carbohydrates, in an attempt to further define this condition.

PLAN OF STUDY

Subjects.—Four subjects with carbohydrate intolerance and one control patient were studied for a total of 17 periods. Comprehensive descriptions of the procedures, methods and mode of charting are presented not only as a basis for evaluation of data herein included but also as a reference for studies to be published later.

The first two subjects were twin girls with histories of poor nutrition and abnormal stools for almost 10 months. Fat absorption was first studied while they received a diet containing milk and cereal.[5]

Liver extract and a crude source of the B complex of vitamins were then administered parenterally while the cereal diet was continued, and fat absorption was determined on two subsequent occasions. After an acute middle ear infection, in both there developed copious diarrhea, and in both a precipitous and considerable weight loss ensued. Complex carbohydrates were then removed from their diet, and two further fat balance periods were obtained. During the latter period both children had occasional episodes of fever and respiratory tract infection, but these were withstood without the development of diarrhea or weight loss (charts 1 and 2).

The third subject was a 1 year old boy with evidence of intestinal malabsorption, as suggested by the history and confirmed by laboratory examinations. He was studied with and without the addition of complex carbohydrates to his diet.

The fourth child was first studied while receiving cereal [5] and milk. Cereal was then removed from his diet and fat absorption determined again. He was then returned to a diet which included cereal, and fat absorption studies were repeated. The last balance period was obtained after two months of a diet free of complex carbohydrates. Data for electrolyte balance were obtained during the first three periods (chart 3). A single period obtained from a normal infant is included for comparison (chart 4).

Methods.—Competent investigators have always agreed that the efficiency of fat absorption can be determined only by quantitative measurement of the amount of fat ingested and excreted.[6] In spite of this, studies still appear in which some

4. Sheldon, W., and MacMahon, A.: Studies in Coeliac Disease: Fat Absorption, Arch. Dis. Childhood **24**:245-249, 1949. Sheldon, W.: Coeliac Disease: A Relation Between Dietary Starch and Fat Absorption, ibid. **24**:81-87, 1949.

5. A commercially available cereal containing wheat, oats and corn starch.

6. Wollaeger, E. E.; Comfort, M. W.; Weir, J. F., and Osterberg, A. E.: Total Solids, Fat and Nitrogen in Feces: Study of Normal Persons and of Patients with Duodenal Ulcer on Test Diet Containing Large Amounts of Fat, Gastroenterology **6**:83-92, 1946. Holt, L. E.; Courtney, A. M., and Fales, H. L.: Fat Metabolism of Infants and Young Children: II. Fat in the Stools of Infants Fed on Modifications of Cow's Milk, Am. J. Dis. Child. **17**:423-439 (June) 1919; Fat Metabolism of Infants and Young Children: III. Fat in the Stools of Children on a Mixed Diet, ibid. **18**:107-126 (Aug.) 1919; Fat Metabolism of Infants and Young Children: IV. Digestion of Some Vegetable Fats by Children on Mixed Diet, ibid. **18**:157-172 (Sept.) 1919. Harrison, G. A., and Sheldon, W. P. H.: Fecal Fat Analysis in Children, Arch. Dis. Childhood **2**:338-348, 1927.

compromise is employed, such as staining of stools or simply expressing the per cent of fat in the stools without comparison with the fat intake.

Long term balance studies are obviously ideal for the study of the metabolism of electrolytes, fat and nitrogen in growing children. In the present study foreperiods of 10 to 15 days were used. It was hoped that after that many days a three to four day collection could be obtained which was a representative sample of the child's metabolism during a steady state. All collections lasted at least three days and some collections for four and five days.

Procedures.—After a suitable foreperiod, 200 mg. of carmine was administered between 7:00 and 10:00 p. m. with the final feeding of the evening. From then

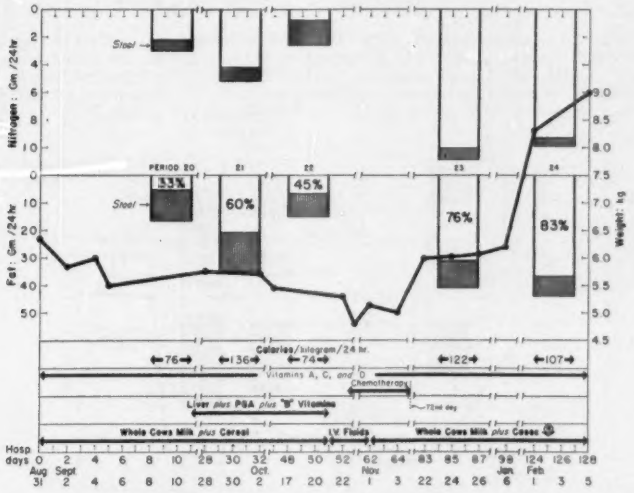

Chart 1.—Intestinal insufficiency (carbohydrate intolerance): effect of complex carbohydrates and parenteral liver therapy on nitrogen and fat absorption (case 1, B. H., UHM 794118, aged 14 months; periods 20 to 24). Diet: period 20, whole cow's milk plus cereal; period 21, similar to period 20, with addition of parenteral liver therapy plus administration of folic acid and B complex of vitamin; period 22, same as period 21; period 23, 23 days after the discontinuation of cereal and 31 days after the discontinuation of parenteral liver therapy, and period 24, 60 days after the discontinuation of use of cereal. Note: (1) stool nitrogen not appreciably increased with increased fat intake. (Compare periods 20 and 21); (2) during period 22, when patient had frank diarrhea, increase of stool nitrogen; (3) per cent fat absorption seeming to improve between periods 20 and 21 but falling off markedly during period 22 (period 23 showed considerable improvement in fat absorption, and this improvement continued to period 24); (4) failure of patient to gain weight between admission and forty-seventh hospital day (frank diarrhea complicated by otitis media caused continued weight loss at end of period 22); (5) the removal of complex carbohydrate and its replacement with calorically equivalent amounts of protein being followed by weight gain in spite of the fact that in periods 23 and 24 total caloric intake was less than it had been in period 21 and (6) persistence of steatorrhea 128 days after hospitalization and 77 days after removal of complex carbohydrate from the diet. Conclusion: Parenteral therapy with liver, folic acid and the B complex of vitamins caused an unsustained improvement in fat absorption and no weight gain while patient was receiving complex carbohydrates. With the removal of complex carbohydrates from the diet an improvement in fat absorption occurred, and it was accompanied by sustained weight gain. This continued in spite of several episodes of respiratory infection.

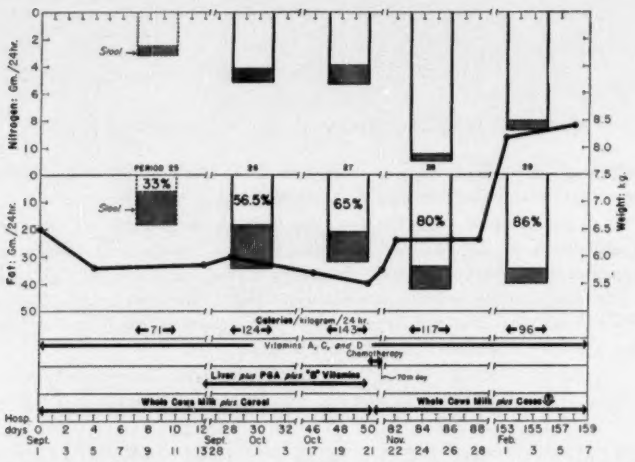

Chart 2.—Intestinal insufficiency (carbohydrate intolerance): effect of complex carbohydrates and parenteral liver therapy on nitrogen and fat absorption (case 2, S. H., UHM 794153, aged 14 months; periods 25 to 29). See legend of twin B. H. (chart 1). A stool specimen was lost during period 25; for purposes of comparison, data from period 20 of patient B. H. have been inserted in period 25.

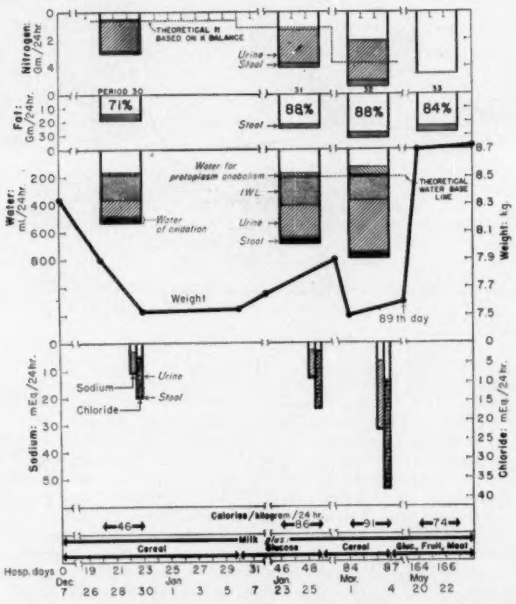

Chart 3.—Intestinal insufficiency (carbohydrate intolerance): effect of complex carbohydrates on electrolyte, nitrogen and fat balance (case 4, D. O., UHM 797785, aged 9 months; periods 30 to 33). Diet: period 30, whole cow's milk plus complex carbohydrates; period 31, whole cow's milk without complex carbohydrates; period 32, whole cow's milk with complex carbohydrates, and period 33, whole cow's milk without complex carbohydrates. Note: (1) in periods 30 and 31, good agreement between the actual nitrogen balance and the theoretical nitrogen balance based on potassium balance; (2) markedly increased potassium balance, period 32, as reflected by the theoretical nitrogen balance; (3) little azorrhea in spite of steatorrhea; (4) failure to demonstrate considerable electrolyte loss in the stools in spite of steatorrhea; (5) greater retention of electrolytes, and more chloride than sodium, by patient while receiving complex carbohydrates; (6) failure of patient to gain weight while receiving complex carbohydrates, and (7) failure of steatorrhea to disappear with the removal of complex carbohydrates, in spite of good weight gain. Conclusion: Inclusion of complex carbohydrate in the diet disturbed metabolism and prevented weight gain.

until 7:00 a. m. the following day nothing but water was allowed by mouth. At 7:00 a. m. urine collections were started, and the first feeding of the collection period was given. Three evenings after the administration of the original carmine dose 200 mg. of carmine was again administered in the same manner. The following day at 7:00 a. m. urine collections were terminated. The first carmine stool passed at the beginning of the period was discarded. At the end of the collection period the first carmine stool passed was kept and added to the pool. The stools were stored in air-tight jars with screw tops and the collection mixed in a Waring blendor,* and an aliquot was analyzed. When water content was to be determined, stools were weighed before blending and duplicate aliquots obtained

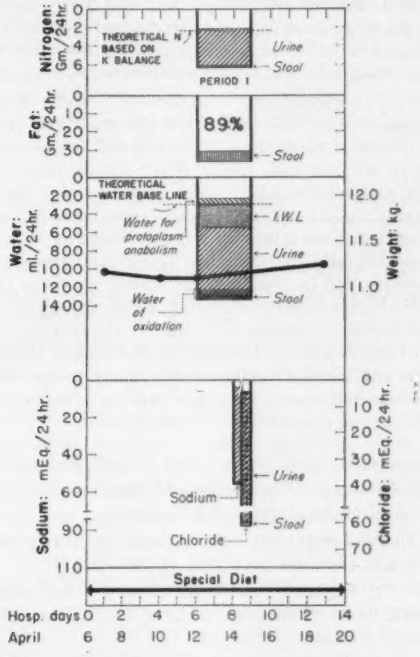

Chart 4.—Electrolyte, nitrogen and fat balance on a cereal-containing diet (case 5, D. J., UHM 790363, aged 11 months). Note: (1) theoretical nitrogen balance based on potassium balance coinciding with actual nitrogen balance, and (2) relation between sodium and chloride intake and retention. Conclusion: The presence of cereal in the diet of a normal child permits retention of potassium in amounts needed for fabrication of protoplasm and retention of sodium and chloride in the ratio in which they exist in extracellular water.

for drying. The mixture was preserved with 10 per cent by volume of a mixture of equal parts of concentrated hydrochloride acid and ethyl alcohol. If analyses for electrolytes were to be included, approximately 18 N sulfuric acid was substituted for the concentrated hydrochloride acid. Dry weight of stools was determined on a blended aliquot taken before the addition of acid.

In male children urine was collected without catheterization by use of a rubber and glass adapter. In female children an indwelling catheter was used. One cubic

centimeter of 14 N sulfuric acid per 100 cc. of expected urine volume was used as a preservative. The urine collection bottle was kept in ice. Analyses for nitrogen and electrolytes were performed after pooling.

All feedings were prepared and supervised by a dietitian.[7] All solids were weighed, and liquids were made to volume in a graduated cylinder. The specific gravity of milk was used in estimating its water content. Refusals were pooled by the dietitian and then subtracted from the intake. Milk, cereal and dextri-maltose[8] were analyzed in the laboratory for nitrogen and electrolytes. The fat content of the milk was determined and kept constant by the distributing dairy.

Stool, urine and diet nitrogen were determined by the micro-Kjeldahl method, with use of a Pregl apparatus. The method of Ma and Zuagaga[9] with the indicator suggested by Sobel and others[10] was employed.

Several of the stools were analyzed late in the study by a macro-Kjeldahl method, with use of the above modification, and agreement with the micromethod was satisfactory. Recoveries and duplicate determinations gave good results.

The sodium and potassium content of diets and excreta were determined on specimens wet ashed after the method outlined by Peters and Van Slyke.[11] Digestion was performed with fuming nitric acid and the amount of sulfuric acid already present in the stool pool, usually 10 per cent by volume. Perchloric acid was required to aid oxidation only in stools with very high fat content. Before potassium was determined, calcium hydroxide was added to ashed samples of stool and diet until they were basic to phenolphthalein, as suggested by Wood.[12] This served two purposes: It neutralized excess acid frequently present, which later caused creeping, and by subsequent filtration it served to remove phosphate, always present in high concentrations, which tended to interfere with evaporation in the platinum crucible. That this in no way interfered with the accuracy of the method was determined by recovery studies. Sodium content was determined by the method of Butler and Tuthill;[13] potassium content, by the procedure of Shohl and Bennett.[14] Chloride content was determined with use of an open Carius method[15] with the modification suggested by Wilson and Ball.[16]

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7. The supervision of this phase of the balance studies was performed by Miss Rosemarie Smith and Miss Elizabeth Lyons.

8. Manufactured by Mead Johnson & Company.

9. Ma, T. S., and Zuagaga, G.: The Micro-Kjeldahl Determination of Nitrogen, Indust. & Engin. Chem. (Analyt. Ed.) **14**:280-282, 1942.

10. Sobel, A. F.; Meyer, M., and Gottfried, S. P.: A Convenient Titrimetric Ultramicromethod for the Estimation of Urea and Kjeldahl Nitrogen, J. Biol. Chem. **156**:355-363, 1944.

11. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Methods, vol. 2, Baltimore, Williams & Wilkins, 1932.

12. Wood, E. H.: Low Temperature Wet Ashing Method Applied to Study of Electrolyte Composition of Ventricular Musculature and Lung Parenchyma of Dog, J. Biol. Chem. **143**:165-170, 1942.

13. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J. Biol. Chem. **93**:171-180, 1931.

14. Shohl, A. T., and Bennett, H. B.: A Micro Method for the Determination of Potassium as Iodoplatinate, J. Biol. Chem. **78**:643-651, 1928.

15. Van Slyke, D. D.: The Determination of Chlorides in Blood and Tissues, J. Biol. Chem. **58**:523-529, 1923.

16. Wilson, D. W., and Ball, E. G.: A Study of the Estimation of Chloride in Blood and Serum, J. Biol. Chem. **79**:221-227, 1928.

Fat determinations were done with a wet extraction method modeled after that of Fowweather [17] as modified by Cushman.[18] Vitamin A and carotene of the plasma were determined by the method of May and others [19] adapted to a Coleman Jr. spectrophotometer.

For duodenal enzyme analysis the following methods were used: trypsin, modified Fermi method; [20] lipase, method of Archibald and Ortiz,[21] and amylase, method of Norby as modified by Lagerlöf.[22]

Method of Charting Data.—Charts presenting the experimental data were prepared largely after the method of Reifenstein and others.[23] The original data from which the charts were prepared are included in tables 1 and 2. The mechanics involved are briefly the following: Intake is charted below the zero line. All increments of outgo are charted in an upward direction, starting at the bottom of the intake line and rising toward the zero line. Balances are indicated as the space between the sum of all sources of outgo and the zero line. If the balance is positive the total output line is below the zero line. If the balance is negative, the total output line is above the zero line.

The following other features should be noted: The "weight" scale is so plotted in relation to the "water" scale that 1,000 Gm. occupies the same space as 1,000 ml.

The sodium and chloride scales are so arranged that when their balances are drawn equal, the ratio of sodium to chloride is that which normally pertains in extracellular fluid.

All electrolyte balance periods were at least three days long. Analyses were performed on the pooled three day collections, but the average balance of sodium and chloride is charted as for one day only.

The per cent fat absorption is indicated in the area that represents fat balance.

Since the figures for water balances were obtained from several theoretical considerations (discussed below), a "theoretical water base line" has been included. This has been drawn through the line which indicates the sum of the water output during the initial period of study and does not include water for protoplasm anabolism. It can be used to compare the changes in water balance through successive periods more accurately than the water balances as actually charted.

Period numbers indicated in the legend of each chart refer to the numbers in tables 1 and 2, the raw data from which the charts were compiled.

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17. Fowweather, F. S.: The Determination of the Amount and Composition of the Fat of Feces: Investigation of "Wet Method" and Comparison with the "Dry" Method, Brit. J. Exper. Path. **7**:7-14, 1926.

18. Cushman, M.: Unpublished data.

19. May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and in Children, Am. J. Dis. Child. **59**:1167-1184 (June) 1940.

20. Fermi, C.: Reagentien und Versuchmethoden zum Studium der proteolytischen und gelatinolytischen Enzyme, Arch. f. Hyg. **55**:140-205, 1906.

21. Archibald, R. M., and Ortiz, P.: Determination of Lipase Activity, J. Biol. Chem. **165**:443-448, 1946.

22. Lagerlöf, H. O.: Pancreatic Function and Pancreatic Disease Studied by Means of Secretin, New York, The Macmillan Company, 1942.

23. Reifenstein, E. C., Jr.; Albright, F., and Wells, S. L.: Accumulation, Interpretation, and Presentation of Data Pertaining to Metabolic Balances, Notably Those of Calcium, Phosphorus, and Nitrogen, J. Clin. Endocrinol. **5**:367-395, 1945.

TABLE 1.—*Carbohydrate Intolerance*

Patient	Age, Mo.	Period *	Date	Therapy and Diet †	Weight, Kg.	Intake per 24 Hours							
						H_2O, Ml.	N, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories/Kg.	Na, mEq.	Cl, mEq.	K, mEq.
Normal control, D. J.....	11	1 (1)	4/12	W. c. m.	11.1	1315	6.18	35	150	97	56.5	63	38.5
			4/15	Cereal	....	....	....	..	...	..	....	..	....
B. H.....	14	2 (20)	8/ 9	W. c. m.	5.5	....	2.97	16.7	45	73	....	..	....
			9/12	Cereal	....	....	....	..	...	..	....	..	....
		3 (21)	9/29	Liver	5.8	....	5.28	35	78	136	....	..	....
			10/ 2	W. c. m.; cereal	....	....	....	..	...	..	....	..	....
		4 (22)	10/18	Liver	5.4	....	2.57	15	48.6	74	....	..	....
			10/21	W. c. m.; cereal	....	....	....	..	...	..	....	..	....
		5 (23)	11/23	W. c. m.	6.0	....	10.9	41	78	122	....	..	....
			11/26	.....	....	....	....	..	...	..	....	..	....
		6 (24)	2/ 1	W. c. m.	8.3	....	9.94	44	61	107	....	..	....
			2/ 4	.....	....	....	....	..	...	..	....	..	....
S. H.....	14	7 (25)	9/ 8	W. c. m.	5.9	....	3.22	18.2	45.5	71	....	..	....
			9/11	Cereal	....	....	....	..	...	..	....	..	....
		8 (26)	9/29	Liver	5.9	....	5.18	34.3	70	124	....	..	....
			10/ 2	W. c. m.; cereal	....	....	....	..	...	..	....	..	....
		9 (27)	10/18	Liver	5.6	....	5.3	32	73	143	....	..	....
			10/21	W. c. m.; cereal	....	....	....	..	...	..	....	..	....
		10 (28)	11/23	W. c. m.	6.3	....	11	42	79	117	....	..	....
			11/26	.....	....	....	....	..	...	..	....	..	....
		11 (29)	2/ 1	W. c. m.	8.2	....	8.65	40	55	96	....	..	....
			2/ 4	.....	....	....	....	..	...	..	....	..	....
S. J.....	11	12	6/ 7	W. c. m.	6.6	....	3.17	17	63	73	....	..	....
			6/10	Cereal	....	....	....	..	...	..	....	..	....
		13	7/16	W. c. m.	6.15	....	12	31	77	144	....	..	....
			7/19	.....	....	....	....	..	...	..	....	..	....
D. O.....	9	14 (30)	12/27	W. c. m.	7.8	530	3.01	18.3	28.5	46	10.6	13.7	17.8
			12/30	Cereal	....	....	....	..	...	..	....	..	....
		15 (31)	1/23	W. c. m.	7.5	683	4.08	25.1	81.4	86	12.8	16.9	24.1
			1/26	.....	....	....	....	..	...	..	....	..	....
		16 (32)	3/ 1	W. c. m.	7.6	791	5.5	32.6	66	91	32	37.5	35.6
			3/ 4	Cereal	....	....	....	..	...	..	....	..	....
		17 (33)	5/20	W. c. m.	8.7	....	4.57	28	69	74	....	..	....
			5/23	.....	....	....	....	..	...	..	....	..	....

* Figures in parentheses refer to periods on the charts.
† W. c. m. indicates whole cow's milk.

TABLE 2.—*Analysis of Urine and Stool Content and Metabolic Balance per Twenty-Four Hours*

Period	Urine/24 Hours					Stool/24 Hours						Balance/24 Hours						
	Vol. Ml.	N, Gm.	Na, mEq.	Cl, mEq.	K, mEq.	H_2O, Ml.	N, Gm.	Fat, Gm.	Na, mEq.	Cl, mEq.	K, mEq.	H_2O, Ml.	N, Gm.	N, Gm./Kg./24 Hr.	% Fat Absorbed	Na, mEq.	Cl, mEq.	K, mEq.
Normal control, 1..	729	3.59	51.8	57.3	30.7	37	0.49	4.06	0.51	0.76	1.87	301	2.10	0.189	89	4.2	4.8	6
2.....	...	....	....	....	....	..	0.77	11.3	....	.....	....	...	....	.....	33	...	...	..
3.....	...	....	....	....	....	..	0.98	14.2	....	.....	....	...	....	.....	59.5	...	...	..
4.....	...	....	....	....	....	..	1.83	8.2	....	.....	....	...	....	.....	45	...	...	..
5.....	...	....	....	....	....	..	0.83	10.1	....	.....	....	...	....	.....	76	...	...	..
6.....	...	....	....	....	....	..	0.77	7.45	....	.....	....	...	....	.....	83	...	...	..
7.....	...	....	....	....	....	..	(0.77)	(11.2)*	....	.....	....	...	....	.....	(33)	...	...	..
8.....	...	....	....	....	....	..	1.07	14.9	....	.....	....	...	....	.....	56.5	...	...	..
9.....	...	....	....	....	....	..	1.57	11.2	....	.....	....	...	....	.....	65	...	...	..
10.....	...	....	....	....	....	..	0.57	8.3	....	.....	....	...	....	.....	80	...	...	..
11.....	...	....	....	....	....	..	0.62	5.5	....	.....	....	...	....	.....	86	...	...	..
12.....	...	....	....	....	....	..	....	8.2	....	.....	....	...	....	.....	51	...	...	..
13.....	...	....	....	....	....	..	....	3.78	....	.....	....	...	....	.....	88	...	...	..
14.....	127	2.22	6.93	10.3	13.2	30.6	0.28	5.3	0.69	0.32	2.9	180	0.51	0.067	71	3.0	3.1	1.7
15.....	254	2.38	9.85	14.8	18.7	25.1	0.33	3.07	0.67	0.35	2.27	211	1.32	0.174	88	2.3	1.7	3.1
16.....	384	3.0	14.75	17.9	22.7	33.8	0.43	3.9	0.35	0.36	3	186	2.07	0.272	88	6.3	9.24	10.0
17.....	...	....	....	....	....	..	....	4.46	....	.....	....	...	....	.....	84	...	...	..

* Loss of stool specimen invalidated data from this period; data inserted are from period 2 (period 20 on chart of twin B. H.).

The explanation for the various calculations necessary to prepare these charts has been carefully discussed by several authors. The following list includes the arithmetical source of the figures used, while the theoretical source can be obtained by reference to the selected reports.[24]

1. Surface area[25] in square meters (M.²) $= \sqrt[3]{(\text{weight})^2} \times (0.1)$
2. Basal caloric requirement = 1,200 calories /M.²/24 hours
3. Insensible water loss (I.W.L.) = 500 ml. /M.²/24 hours
4. Grams nitrogen in urine = grams nitrogen burned
5. (Line 4) (6.25) (4.1) = calories from protein
6. (Line 4) (6.25) (0.4) = water of oxidation (in milliliters) from protein
7. (Carbohydrate intake, Grams) (4.1) = calories from carbohydrate
8. (Carbohydrate intake, Grams) (0.5) = water of oxidation (in milliliters) from carbodydrate
9. Line 2 — line 5 — line 7 = calories obtained from fat
10. $\frac{\text{Line } 9}{9.3}$ = Grams fat burned
11. (Line 10) (1.07) = water of oxidation (in milliliters) from fat
12. Line 6 + line 8 + line 11 + oral water intake (in milliliters) = total water intake (in milliliters)
13. $\frac{\text{Potassium balance}}{2.7}$ = theoretical nitrogen balance (in Grams)
14. (Grams nitrogen balance) (6.25) = Grams protein formed
15. (Grams nitrogen balance) (32) = Grams protoplasm formed
16. Line 15 — line 14 = water (in milliliters) required for protoplasm anabolism

RESULTS

The results are portrayed in graphic form in charts 1 to 4, and the original data appear in tables 1 and 2. Commentaries on the data and the conclusion drawn therefrom are presented in legends under the charts. The results from patient S. J., with carbohydrate intolerance, are given in tables 1 and 2 but are not presented in graphic form. It may be seen that the findings on this patient confirm those illustrated for patients B. H., S. H. and D. O. in charts 1, 2 and 3.

COMMENT

Although adequate electrolyte balance data for children with carbohydrate intolerance have not come to our attention, we have sought an approximation in studies of children suffering from *Mehlnährschaden*. This was a disease seen mainly during the early part of the twentieth century, when knowledge of appropriate infant dietaries was meager,

24. Newburgh, L. H.; Johnston, M. W., and Newburgh, J. D.: Some Fundamental Principles of Metabolism, Ann Arbor, Mich., Edwards Bros. Inc., 1945. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Interpretations, vol. 1, ed. 2, Baltimore, Williams & Wilkins, 1946. Footnote 23.

25. Lissauer, W.: Über Oberflächenmessungen an Säuglingen und ihre Bedeutung für den Nährungsbedarf, Jahrb. f. Kinderh. **58**:392-411, 1903.

and it was well described and discussed by Czerny and Keller [26] and others.[27] It was an affliction apparently due to a diet excessive in or composed chiefly of complex carbohydrates. Clinically, the patients were atrophic; they had frequent bulky foul stools, anorexia and occasionally edema and distended abdomens and responded to a dietary in which milk replaced *Mehl*.

The reason for the development of wasting in these infants was not known, nor was the existence of steatorrhea established. The fact that their diet had been low in fat, nitrogen, chloride and ash and excessive in complex carbohydrates, however, was noted. Of particular interest to Keller and others was the fact that their urine was frequently chloride free and administered sodium chloride was almost quantitatively retained.[28] No total balance studies were performed, but that electrolyte aberrations occurred may be inferred from tissue analyses.

Frank and Stolte [28] analyzed livers of two children dying of *Mehlnährschaden* and compared the composition of these with that of a newborn infant and that of a child dying of eczema.

We have recalculated their data for comparison with more recent analyses of normal adult liver.[29] It was found that in two patients with *Mehlnährschaden* the electrolyte concentrations expressed as milliequivalents per 1,000 Gm. of wet liver were potassium, 51.4 to 52; chloride, 49.3 to 54, and sodium, 74 to 76. The values in a normal newborn infant and in a patient dying of eczema were respectively potassium, 69 to 65; chloride, 35 to 36.4, and sodium, 52 to 54. Normal adult values are potassium, 55; chloride, 45, and sodium, 82. The corresponding figures similarly calculated from analyses by Steinitz and Weigert [30] on muscle of a patient dying of *Mehlnährschaden* were potassium, 48.5; chloride, 64.5, and sodium, 89.5. Normal muscle values [31] are potassium, 109; chloride, 13.7, and sodium, 18.9. It is evident that there is an increase in sodium and chloride content and a decrease in potassium content in the liver and muscle of persons dying of *Mehlnährschaden*. The increase in sodium and chloride in the liver and muscle

26. Czerny, A., and Keller, A.: Des Kindes Ernährung, Ernährungsstörungen und Ernährungstherapie; Ein Handbuch für Ärzte, Leipzig, 1917, F. Deuticke, chap. 3, pp. 582-604.

27. Salge, B.: Ein Beitrag zur Pathologie des Mehlnährschadens der Säuglinge, Jahrb. f. Kinderh. **76**:125-142, 1912. Czerny, A., and Steinitz, F.: Pathology of Metabolism in the Child, chap. 7, in von Noorden, C.: Metabolism and Practical Medicine, Chicago, W. T. Keener & Co., 1907.

28. Frank, A., and Stolte, K.: Beitrag zur Kenntnis des Mehlnährschadens, Jahrb. f. Kinderh. **78**:167-176, 1913.

29. Shohl, A. T.: Mineral Metabolism, American Chemical Society Monograph Series, no. 82, New York, Reinhold Publishing Corporation, 1939.

30. Steinitz, F., and Weigert, R.: Über die chemische Zusammensetzung eines ein Jahr alten atrophischen und rachitischen Kindes, Monatsschr. f. Kinderh. **4**:301-307, 1905.

31. Darrow, D. C.: Body Fluid Physiology: The Relation of Tissue Composition to Problems of Water and Electrolyte Balance, New England J. Med. **233**: 91-97, 1945.

might have been in part a reflection of expanded extracellular fluid volume associated with edema, but the water content of the tissue by analysis was apparently not excessive. Nor can the excess sodium be explained merely by assuming that it had entered the cells to replace potassium, for, judging by the chloride values, much sodium must have remained extracellular.

Though there are limited facts to support the supposition and though we are lacking evidence of steatorrhea in patients with *Mehlnährschaden,* it seemed possible to suppose that *Mehlnährschaden* might be the extreme form of carbohydrate intolerance. Balance studies performed on patients with carbohydrate intolerance might be expected to demonstrate (1) retention of sodium and chloride in excess of the requirement for formation of extracellular water, (2) retention of relatively more sodium than chloride and (3) a potassium balance lower than that expected to be necessary for formation of intracellular water.

With this background, we may now examine the electrolyte balance of a normal subject and one on whom a diagnosis of carbohydrate intolerance had been made.

In the normal child on a diet containing cereal, the sodium and chloride were retained in the proportion in which they exist in extracellular fluid and the theoretical nitrogen balance based on potassium balance coincided with the actual nitrogen balance. In the patient with carbohydrate intolerance, examination of the second and third periods will permit the following observations: When there were no complex carbohydrates in the diet, except for the existence of steatorrhea, the pattern of balance was similar to that seen in the normal child. However, the addition of cereal to the regimen altered particularly the pattern of electrolyte retention. The total sodium and chloride retention increased, but the chloride retention increased more than the sodium retention. This suggests that if the chloride remained extracellular, sodium had to leave the cells and extra potassium had to go into the cells. That this may have actually happened is suggested by the excess of the theoretical nitrogen balance based on potassium balance over the actual nitrogen balance. These changes, while impressive, are not those which one might have anticipated were *Mehlnährschaden* identical with carbohydrate intolerance, the major difference being noted in the potassium balance.

Our observations concerning the deleterious effect of complex carbohydrates on the fat absorption of this type of patient are similar to the more extensive ones presented by Sheldon and MacMahon.[4]

SUMMARY

In three patients with evidence of intolerance to complex carbohydrates it has been possible to observe the effects of complex carbohydrates on the absorption of fat and nitrogen. In a fourth patient observations were extended to include electrolyte and nitrogen balance data for comparison with the values obtained in a single normal child.

It was possible to demonstrate that while complex carbohydrates were consumed fat absorption was abnormal. This aberration persisted in two of the subjects in spite of the concomitant administration of crude liver extract. There was improvement in fat absorption when complex carbohydrates were removed from the diet.

In the patient on whom electrolyte balance were also obtained, a pattern of retention quite different from the normal was observed when complex carbohydrates were added to the diet. In this subject the changes in fat absorption were not as extreme as those noted for the other three patients.

REPORT OF CASES

Two 14 month old white female twins were admitted to the University Hospitals because of edema and failure to gain weight for seven months.

The family history indicated that both parents, 29 years of age, were living and well. A maternal great uncle had asthma, and both the patients' father and his brother had suffered from atopic dermatitis. A paternal uncle had died of "dropsy" at 5 years of age. The patients' mother had lost one child through a miscarriage several months preceding her next pregnancy. The cause of this was unknown.

The children were born after induced labor following an eight month gestation period. During the third month of pregnancy the mother had received "shots" because of threatened abortion, and at seven months there was slight albuminuria and ankle edema.

CASE 1.—B. H. was the first of the twins to be born and had no neonatal distress. She weighed 2,700 Gm. and was 50 cm. long. Formula feeding of similac® was immediately started. At 2 weeks of age administration of a commercial multivitamin preparation was begun and its use continued until 10 months of age. She raised her head at 2 months, sat at 6 months, stood at 7 months and at 9 months walked with assistance. Her first lower incisors appeared at 6 months.

The onset of the present illness was difficult to date. At 3 months of age vomiting, apparently secondary to abdominal cramps, developed. She also cried frequently and had diarrhea. At 3 months of age an evaporated milk formula was introduced. At 4 months of age a homogenized whole milk formula was introduced and its use continued to 10 months of age. Occasionally because of loose stools or vomiting the mother changed the formula to boiled skim milk, lactic acid milk or protein milk. At 13 months the child was given a formula of homogenized milk, dietene® and an egg. This was continued up to the time of admission. Cereal was introduced at 2 months, and fruits and vegetables, particularly peas, applesauce and beans, as well as rice, wheat and barley, at 3 months. Strained meats were added after 7 months, and practically an unlimited dietary was used after 11 months. At 10 months administration of large doses of vitamin C was started, and iron medication was given intermittently from 8 months to 1 year of age.

At 7 months of age the patient had a "cold" which lasted about 10 days and was accompanied with some looseness of the bowel movements. Two months later she had a similar incident lasting about two weeks, with anorexia, weight loss and a change in stool habits.

There had always been great variations in the nature and the frequency of the stools. During the first weeks of life the patient had two to three formed stools a day, but occasionally the stools were very large. By 9 months of age occasional diarrhea occurred. The stools were frequently very large, and the odor was foul. A single episode of frank diarrhea that lasted three weeks occurred during the tenth month of life.

From then on the patient had occasional diarrhea, with large foul-smelling stools, three to four a day. Changes of formula seemed to have no effect on them. At 11 months of age, because of the abnormal appearance of the stools, the child was given 0.5 Gm. of pancreatin a day. The administration was discontinued after two weeks because of the apparent ineffectivness of the drug. For the four months previous to admission the child had been anorexic, irritable and obviously failing. Edema appeared one week before admission and then was noted only on her feet. The patient's weight at 3 months was 5,500 Gm.; at 6 months, 7,000 Gm.; at 10 months, 5,300 Gm., and at 1 year, 6,400 Gm.

At the time of admission to the University Hospitals her weight was 6,000 Gm. The patient was a thin, obviously emaciated, chronically ill infant. There was moderate edema of the face, the eyelids and the dorsa of the feet. The skin was pale and shiny in the areas of edema and hung in loose folds over the buttocks and the forearm. The fontanel was 2 by 3 cm. The mucous membrane of the mouth and the lips was clean. Four upper and two lower incisors were present. There was slight shotty cervical adenopathy but no costochondral beading. The thoracic cage was without deformity. The abdomen was protuberant, with poor muscle tone and obvious patterning of the bowel. To palpation it was quite doughy. Muscle tone of the extremities was poor.

Laboratory studies on admission revealed the following facts: The urine was normal. The hemoglobin level was 9.7 Gm. per 100 ml.; there were 2,800,000 red blood cells and 4,900 white blood cells, with 39 per cent segmented granulocytes (polymorphonuclear leukocytes), 58 per cent lymphocytes and 3 per cent monocytes. A blood smear showed marked anisocytosis and poikilocytosis. The fasting blood sugar level was 54 mg. per 100 ml. The serum protein content was 4.2 Gm. per 100 ml. (albumin 2.3 Gm. and globulin 1.8 Gm.). The calcium level was 7.3 Gm., the phosphorus level 2.9 Gm. and the alkaline phosphatase activity 7.9 Bodansky units per 100 ml.

After transfusion the hemoglobin level and red blood cell count improved until at the time of discharge the hemoglobin level was 12.9 Gm. per 100 ml. Analysis of the duodenal enzymes showed essentially normal lipase and trypsin and some decrease in amylase. The oral glucose curve showed a fasting level of 61 mg. per 100 ml., with a peak of 72 mg. at one hour. Liver function studies showed normal conditions, with a sulfobromophthalein test showing but 1 per cent retention in 45 minutes. A bone marrow aspiration showed a normoblastic red cell series with some macronormoblasts; the marrow was otherwise normal. A vitamin A absorption test showed a fasting level of vitamin A of 78 micrograms per 100 ml., with a rise at three and five hours to 138 micrograms of vitamin A per 100 ml. The carotene level was 10.5 micrograms per 100 ml.

Cultures of stools on four occasions failed to reveal any pathological organisms. Roentgen examination of the gastrointestinal tract showed considerable clumping of the barium and evidence of spasm and dilatation of the intestine. Roentgen examination of the sinuses failed to show any evidence of infection. Although the bone age was not particularly abnormal, there was some demineralization.

After admission to the hospital, the child was started on a diet of whole cow's milk and cereal. Within the first two weeks she received two transfusions of whole blood. Vitamins A, C and D in adequate amounts were administered with her formula. During the first eight days there was a marked loss of weight which was accompanied with the disappearance of edema. From the ninth to the twelfth day of hospitalization fat absorption studies were performed; it was found that but 33 per cent of the administered fat was absorbed. While the same diet was continued, folic acid, crude liver and the B complex of vitamins were administered parenterally to the patient. After 15 days of this therapy, fat absorption studies were again undertaken, and it was found that absorption had increased to 60 per cent; however, there had been very little weight gain.

During the next 20 days this therapy was continued and the patient began to lose weight. On the fifty-third day of hospitalization frank diarrhea began; the

patient became febrile, and it was apparent that a middle ear infection had developed. Parenteral fluid therapy was necessary, and sulfadiazine, penicillin and streptomycin were used as indicated in the chart, with the improvement of the patient by the sixty-third day of hospitalization. Cereal was removed from the regimen, and penicillin and sulfadiazine administration was continued for 10 days longer. With remarkable rapidity the child began to gain weight, and a fat balance period conducted 22 days after the removal of cereal from the diet showed 76 per cent fat absorption. At that time the patient had gained to 6,200 Gm. After two months on a starch-free diet, the patient's fat absorption was 83 per cent, and at that time she weighed 8,300 Gm. One month later her weight had increased to 10,100 Gm.

Case 2.—S. H. was born the second of twins and required oxygen immediately after delivery. The birth weight was 2,200 Gm., and the child was 48 cm. long. Her initial formula was prepared from a proprietary powdered milk, but after several weeks diarrhea developed. On this account, the formula was changed to skim milk, without much benefit, and at 2 months of age a protein milk formula was used. After two weeks this was changed to lactic acid milk, and at 3 months of age an evaporated milk formula was introduced. This was continued for the next six months. At 13 months of age a formula made of homogenized milk, dietene® and an egg was used, and its use was continued up to the time of hospitalization.

Solid foods, in the form of cereal, were introduced at 2 months of age. Fruits and vegetables were given after 3 months, and at 7 months eggs and meat were offered. By 12 months the child was on an essentially complete diet.

Administration of a commercial multivitamin preparation was started at 2 weeks and continued for a year. At 10 months of age large doses of vitamin C were administered. Two desultory attempts to administer iron, at 8 and 10 months, were recorded, but the mother did not remember the amount of medication given. At 8 months of age the patient received 100 mg. of pancreatin a day for two weeks. This was without any obvious benefit to the patient and its use was discontinued.

The child's stools became frequent and soft after a month and a half of life. At about 2 months of age the child began to vomit once or twice daily and continued to do so intermittently until the time of admission. Occasionally she was benefited by formula change. At 7 and 9 months of age the patient had two respiratory infections which lasted about two weeks. These were accompanied with anorexia, weight loss, irritability and increase in number of bowel movements. From 3 to 7 months of age the patient had two to three regular bowel movements a day, with stools apparently normal in size and odor. After 10 months of age, stools began to smell bad and became unusually large. At 12 months of age there was occasional diarrhea and undigested parts of food were observed in the elimination. The appetite had been good, but after 10 months of age it became poor. In the month preceding admission the patient seemed to enjoy eating solids but consistently refused three fourths of her formula. At 3 months of age the patient weighed 4,700 Gm.; at 6 months, 6,400 Gm.; at 11 months, 5,300 Gm., and at 1 year, 6,500 Gm.

Physical examination at the time of hospital admission, at 14 months of age, revealed a critically ill child. Her weight was 6,500 Gm. There was obvious wasting of subcutaneous tissue of the arms, wrists and thighs and moderate edema of the dorsa of the feet. The skin was pale and waxy and drawn tightly over the edematous area. The fontanel was patent and flat. Mucous membranes of the mouth were normal, and there were 10 teeth present. No deformity of the thoracic cage could be demonstrated. The abdomen was distended, soft and atonic. No organ or masses were felt, and there was definite patterning of the intestine. No evidence of infection was noted.

Laboratory findings revealed the following information: The urine throughout hospitalization was consistently normal. At the time of admission the hemoglobin level was 10.6 Gm. per 100 ml. The red blood cell count was 4,800,000, the white blood cell count, 7,700, with 29 per cent segmented granulocytes (polymorphonuclear leukocytes) and 71 per cent lymphocytes. There were marked anisocytosis and poikilocytosis present in a smear. The serum protein level was 3.7 Gm. per 100 ml.,

with 2.2 Gm. of albumin and 1.5 Gm. of globulin. The calcium level was 6.5 Gm. per 100 ml. Numerous stool cultures failed to reveal any pathogenic organisms. The oral glucose tolerance test showed a fasting level of 78 mg. per 100 ml., with no change in this concentration for the next three hours. Vitamin A absorption tests showed a fasting level of 78 micrograms per 100 ml., with a peak at five hours of 138 micrograms. The fasting level of carotene was 10.5 micrograms per 100 ml. A bone marrow aspiration showed a normoblastic and macronormoblastic red cell series, with normal polymorphonuclear leukocytes.

Analysis of the duodenal enzymes showed normal trypsin, lipase and amylase. Liver function studies failed to reveal any abnormalities, and a sulfobromophthalein test showed 2 per cent retention in 45 minutes. A tuberculin test with 0.1 mg. of old tuberculin gave a negative reaction in 48 hours.

Roentgen examination of the chest and sinuses failed to demonstrate any evidence of infection. Roentgen examination of the bones, although revealing demineralization, showed normal epiphysial maturation.

The gastrointestinal tract examination with barium showed considerable clumping, with areas of spasm and dilatation of the intestine, but was not otherwise remarkable.

After admission to the hospital, the patient was given a diet of whole cow's milk and cereal. Vitamins A, C and D in appropriate amounts were administered. Four transfusions were given during the first three weeks. Fat absorption studies done during the second week in the hospital were invalidated because a specimen was lost. However, on the chart of her course we have indicated the per cent of absorption of her sibling for use as an appropriate estimation. After two weeks in the hospital, parenterally administered liver, folic acid and the B complex vitamins were introduced into her regimen. Fat absorption studies were repeated after two and four weeks of this therapy, and the absorption had changed from 56.5 per cent to 65 per cent. There was an initial weight loss of 700 Gm., attributed to loss of edema, and during the first 50 days of hospitalization the patient did not gain weight. During the eighth week of hospitalization there was a precipitous decline in her condition associated with diarrhea and fever. Its cause was found to be an otitis media and respiratory infection. Penicillin, sulfadiazine and streptomycin therapy were used. After relief of the diarrhea, administration of the vitamin B complex, liver and folic acid were discontinued and the cereal was removed from the diet. The caloric equivalent of cereal was introduced in the form of casein. Fat absorption was tested 35 days after this change of therapy and had improved to 80 per cent. At that time the patient's weight was 6,200 Gm. The weight gain had been almost 1,500 Gm. from its lowest point. Three and a half months later while on the same regimen her fat absorption had improved to 86 per cent, and her weight was then 8,200 Gm.

CASE 3.—S. J., a 1 year old white boy, was admitted to the University Hospitals because of respiratory tract infections for eight months, failure to gain weight for periods of six months and fever, diarrhea and vomiting of 10 days' duration.

His mother's pregnancy, the delivery and the neonatal period were all normal, and early weight gain was adequate.

At about 4 months of age a respiratory tract infection occurred, and this responded to appropriate therapy. There were at least six similar episodes previous to hospitalization, characterized each time by rhinorrhea, fever and pharyngitis.

The formula during the neonatal period was composed of evaporated milk and corn syrup. At 6 weeks of age cereals were started, and at 3 months vegetables and fruits were introduced into the dietary.

At 11 months of age the patient's abdomen was noted to be enlarged, and he commenced passing two or three large watery stools each day. Liver extract was administered parenterally, without benefit, and a diet of bananas and milk and cereal was poorly tolerated.

At the time of admission the patient weighed 7,000 Gm.; he was afebrile and looked wasted and chronically ill. His abdomen was protuberant though not tense,

and the liver was palpable 2 cm. below the right costal margin. No evidence of infection was noted.

The hemoglobin level was 12.6 Gm. per 100 cc. The white blood cell count was 16,100, with 52 per cent lymphocytes, 46 per cent segmented granulocytes (polymorphonuclear leukocytes), 1 per cent eosinophils and 1 per cent monocytes. Results of numerous urine examinations were within normal limits. The blood urea nitrogen level was normal, as were the determinations of duodenal enzymes. An oral glucose tolerance test showed a maximum rise of 30 mg. per 100 cc. A vitamin A absorption test showed a poor rise, and the blood carotene level was only 10.5 micrograms per 100 cc. (normal, 100 micrograms per 100 cc.). The levels of sodium, chlorine, potassium, calcium, phosphorus and phosphatase in the blood were within the normal range.

The roentgen examination of the wrists showed some retardation of carpal ossification. There was minimal evidence of pulmonary infiltration. The examination of the gastrointestinal tract failed to demonstrate any congenital anomalies or signs of obstructive lesions.

His hospital course was characterized during the first few weeks by subnormal temperatures. Two weeks after admission because of a persistent leukocytosis, the presence of pulmonary infiltration, as shown by roentgenograms, and the hypothermia, penicillin therapy was begun, with some benefit. This was discontinued after two weeks.

Balance studies were done during the third week of hospitalization when the patient was receiving cereal as well as whole milk. He tolerated this dietary poorly and at the end of the collections was given a diet free of complex carbohydrates. In spite of this alteration and although his clinical condition appeared good, his weight gain was poor.

Observations during a second balance period, after one month of a cereal-free diet, showed striking improvement in fat absorption. During this period there was also added to the formula the amount of phosphatase normally present in milk which is destroyed by pasteurization (about 10 Bodansky units). It was not felt that this contributed in any way to the patient's improved absorption, since during a third balance period, when cereal was reintroduced into the diet and the phosphatase kept in the milk, not only did he lose weight but the profound steatorrhea returned.

He was finally discharged almost four months after admission, having been on a cereal-free diet for one month and having gained 500 Gm. during that time. Two months later, while on the same diet, he had gained almost 3,000 Gm.

Case 4.—D. O., an 8 month old white boy, was brought to the University of Minnesota Hospitals because of persistent cough of four months' duration. The child had received care from a welfare agency from 2 weeks of age until the time of admission, and nothing was known about the mother's pregnancy or his early neonatal course. His birth weight was not known.

The patient has been well until 4 months of age, at which time there developed what was apparently an infection of the upper respiratory tract, with fever, foul stools and cough. From then until the time of admission there was almost continual evidence of respiratory tract infection, with otitis media and pneumonitis. Therapy with antibiotics succeeded in relieving most of the evidence of infection.

Starting at 4 months of age, the child had had an increasing number of periods during which the stools were large, frothy, foamy and foul smelling. These occasionally improved when the respiratory tract infections remitted; however, from 5 months to the time of admission the stools were never really normal. No therapy directed at this phase of his disease had been used.

At the time of admission the patient weighed 8.5 Kg., his rectal temperature was 99.8 F. and his length was 74 cm. He was a fairly well developed, moderately well nourished, alert child. He sat well and could barely pull himself to the standing position. The pharynx was slightly injected, and the tonsils were somewhat enlarged

and bulky. There were no abnormal findings in the chest or ears. The hemoglobin concentration was 10.7 Gm. per 100 ml., the white blood cell count was 8,700, with 45 per cent polymorphonuclear leukocytes, 46 per cent lymphocytes, 7 per cent monocytes and 2 per cent eosinophils. The urine examination revealed no abnormalities. The result of a tuberculin test with 0.1 mg. of old tuberculin was negative. The results of both the Kline and the Wassermann tests for syphilis were negative. Roentgen examination of the chest failed to reveal any evidence of infiltration or infection. Determination of trypsin, lipase, and amylase in the duodenal juice revealed that the first two were normal and that amylase activity was slightly decreased. Roentgen examination of the wrists showed normal bone maturation. There were metaphysial changes consistent with early mild rickets. The child's course during hospitalization and study was characterized by repeated episodes of infection of the respiratory tract. These were treated vigorously with chemotherapy. Characteristically, he had one large foul loose stool a day, but there was no evidence of frank diarrhea.

After an adequate foreperiod, fat absorption data were obtained while the patient was receiving a diet of whole milk plus cereal. The cereal was then removed from the diet and fat absorption redetermined. After the completion of these periods, cereal was again added and the fat absorption studied again. The weight gain was impressive when cereal was removed from the diet, but the patient seemed unable to gain while it was included. He was discharged to his foster home on a diet which did not include complex carbohydrates.

He was readmitted to the hospital two months later for reevaluation. During the interim period he had gained over 1,000 Gm. On physical examination he was found to be considerably improved, with good muscle tone. There was no evidence of infection, and abdominal distention was not remarkable. Fat absorption studies were done, and the patient was discharged, receiving a more liberal diet, which still contained no complex carbohydrates.

CASE 5.—The patient, D. J., was the product of a normal full term pregnancy terminating in spontaneous delivery. He was referred to the University Hospitals at 2 weeks of age because of a deformity of his left foot. At that time he weighed 3,600 Gm. Physical examination demonstrated no abnormalities other than a talipes equinovarus deformity of the left foot, with a supernumerary fifth digit. He was treated at the University Hospitals with the application of a plaster cast to the deformed foot.

At 10 months of age he was readmitted to the hospital for removal of the supernumerary digit. At that time he weighed 10,500 Gm. and was found to be a well developed, well nourished infant. There were no deformities or abnormalities noted other than those relating to his left foot.

Two weeks after an operation, the metabolic data reported herein were obtained.

Progress in Pediatrics

PHYSIOLOGICAL DEVIATIONS OF THE PREMATURE INFANT

With Summary of Principles of Care

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IMPORTANCE OF THE PROBLEM OF PREMATURE BIRTH

Infant Mortality.—In the last few decades there have been a tremendous reduction in mortality rates and a great extension in life expectancy. It is apparent that the increase in life expectancy has been due more to a reduction in infant mortality

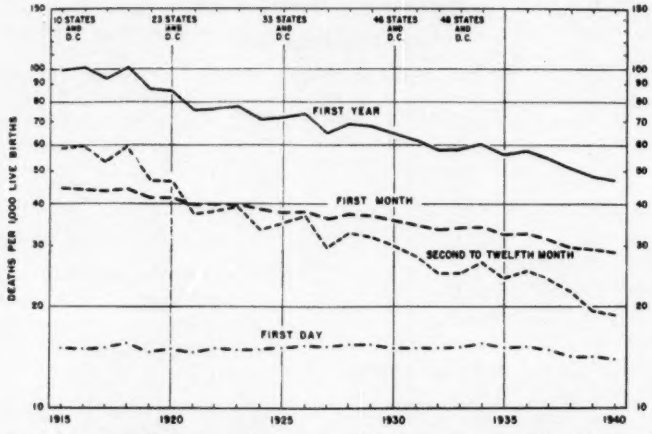

Fig. 1.—Infant mortality rates, by age, in United States expanding birth-registration area, 1915 to 1940. From United States Department of Labor, Children's Bureau, chart no. IM 40-3. Based on data from United States Bureau of the Census.

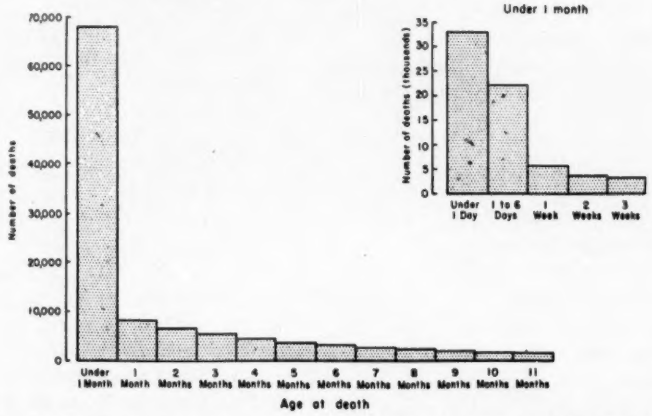

Fig. 2.—Infant deaths, by age in months, in the United States in 1940. From United States Department of Labor, Children's Bureau, chart no. IM 40-2. Based on data from United States Bureau of the Census.

than to anything else. If we study mortality figures for infants, as shown in figures 1 and 2, we see a great reduction except in the neonatal period. There has been little reduction in mortality in the immediate neonatal period, for instance, the first day, and not much in the first month, the greatest improvement being in the age groups from 2 to 12 months.

From 1940 through 1942 there has been a noticeable drop in death rate during the first day of life which may have been related to improved maternal health. In an analysis of figures of the United States Bureau of the Census for the 10 years 1933 to 1943, Gooch [1] noted that the neonatal mortality (for the first month of life) rate declined 27 per cent.

TABLE 1.—*Infant Deaths Per 1,000 Live Births* [1]

	First Year	First Month	First Day
1933	58.1	34.0	15.1
1943	40.4	24.7	11.6
Per cent change	—30.5	—27.4	—23.2

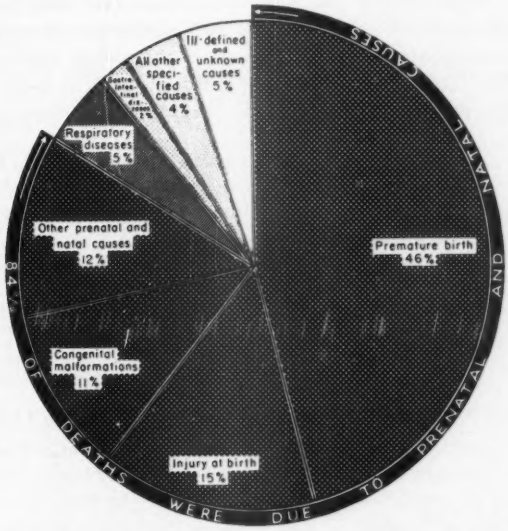
84% OF DEATHS WERE DUE TO PRENATAL AND NATAL CAUSES
Premature birth 46%
Injury at birth 15%
Congenital malformations 11%
Other prenatal and natal causes 12%
Respiratory diseases 5%
All other specified causes 4%
Ill-defined and unknown causes 5%

Fig. 3.—Causes of neonatal death by percentage distribution in the United States in 1940. From the United States Department of Labor, Children's Bureau, chart no. IM 40-5. Based on data from United States Bureau of the Census.

If one breaks down neonatal mortality into its various causes (fig. 3), one sees that a large part, nearly one half, is made up of deaths ascribed to prematurity.

Definition of Prematurity.—The definition of prematurity is confused. The premature infant is considered to be any baby less than 5½ pounds (2,500 Gm.) in weight and less than 18 inches (45.7 cm.) in length, with a head circumference of less than 13 inches (33 cm.) and with a gestation period of 28 to 37 weeks. These criteria are as defined by the United States Bureau of the Census and the Children's Bureau, and one must adhere to them for statistical purposes. However, because of the physiological response to the temperature and humidity of the environ-

1. Gooch, M.: Ten Years of Progress in Reducing Maternal and Infant Mortality, with Figures Showing Changes in Rates Between the 2 Years 1942-1943, Child **10**:77, 1945.

ment, a weight of 5 pounds (2,270 Gm.) seems a more practical point at which to change the nursing and medical program. Whatever weight we choose is arbitrary and does not measure what we really want to measure, that is, the degree of immaturity. Signs of immaturity include the friable texture of the finger nails, roentgenologic evidence of lack of the ossification center of the proximal tibial epiphysis, lack of subcutaneous tissue, the fragility of the skin texture, the lack of activity, the inability of the baby to maintain its own body temperature, the inability to nurse, the feeble cry, the persistence and severity of jaundice and the lack of resistance to infection.

For example, a skinny 3 pound (1,360 Gm.) baby crying vigorously who can maintain its temperature easily and take its food with good appetite is less immature and has a better chance to survive than another baby weighing 4 pounds (1,814 Gm.) who is sluggish, has a gelatinous translucent skin, bruises easily and has primitive finger nails. There are also racial differences in maturity of infants. Small Negro infants are often physiologically maturer than white infants of comparable weight. There are sex differences within all races, as well. Female infants may be maturer per unit of weight or by "bone age" than male infants.

TABLE 2.—*Number and Percentage of Premature Babies at Various Weights* [3]

	Births in New York City, 1939		Hospital Births in New York City, 1945	
Weight Group	Number	Per Cent	Number	Per Cent
Less than 1,000 Gm.	370	5.07	457	4.46
1,000 to 1,499 Gm.	582	7.98	700	6.83
1,500 to 1,999 Gm.	1,326	18.19	1,824	17.81
2,000 to 2,499 Gm.	5,013	68.76	7,263	70.90
Total	7,291	100.00	10,244	100.00

Incidence of Prematurity.—The total incidence of premature birth in the United States is not known, but an estimate based on reports from several cities reveals an incidence of premature live births of between 7 and 11 per cent. The number and percentage of premature infants at various weight levels born in New York city in 1939 [2] and in hospitals in New York in 1945 (Department of Health) [3] are shown in table 2.

Mortality of Premature Infants.—Almost all (97 per cent) the deaths attributed to premature birth occur during the first month of life, with 57 per cent occurring in the first day.[4]

Dunham [5] has noted in table 4 a 23 per cent decrease in neonatal mortality rate for premature births in a 10 year period.

The cause of death may be difficult to determine in premature infants. Atelectasis is not an acceptable cause of death (see section on "Respiration"). Table 5 reveals

2. Duffield, T. J.; Parker, S. L., and Baumgartner, L.: Birth Weight and Its Relation to Neonatal Mortality: An Analysis of Data on Live Births in New York City in 1939, Child **5**:123, 1940.

3. Dunham, E. C.: Premature Infants: A Manual for Physicians, Publication no. 325, United States Federal Security Agency, Children's Bureau, 1948, p. 12.

4. Dunham,[3] p. 38.

5. Dunham,[3] p. 36.

that in 35 per cent of babies considered viable by Potter's classification, the cause of death could not be determined.

It is difficult to compare the mortality figures for prematurity of one institution with those of another. When this is attempted, we have to ignore the varying

TABLE 3.—*Deaths* from Premature Birth, by Age (Exclusive of Stillbirths)* [4]

Age at Death	Number	Per Cent	Deaths per 1,000 Live Births
Under 1 day	18,909	57.1	6.7
1 day to under 1 wk.	9,750	29.4	3.5
1 wk. to under 1 mo.	3,406	10.3	1.2
1 mo. to under 1 yr.	1,055	3.2	0.4
Total	33,120	100.00	11.8

* Based on data from United States Bureau of the Census. Data are for continental United States (1944).

TABLE 4.—*Deaths* in First Month of Life from All Causes and from Premature Birth (Exclusive of Stillbirths)* [5]

	Deaths per 1,000 Live Births		Per Cent Change from Preceding Year	
Year	All Causes	Premature Birth	All Causes	Premature Birth
1935	32.4	14.9	.....	.....
1936	32.6	15.1	+0.6	+1.3
1937	31.3	14.8	—4.0	—2.0
1938	29.6	13.8	—5.4	—6.8
1939	29.3	13.8	—1.0	0
1940	28.8	13.3	—1.7	—3.6
1941	27.7	12.8	—3.8	—3.8
1942	25.7	11.9	—7.2	—7.0
1943	24.7	11.4	—3.9	—4.2
1944	24.7	11.5	0	+0.9

* Based on data from United States Bureau of the Census. Data are for continental United States, 1935 to 1944.

TABLE 5.—*Neonatal Deaths of Previable and Premature Infants* and Causes of Death as Determined by Postmortem Examination (Potter)*

	Total			
Cause of Death.	Number	Per Cent	Previable	Premature
No abnormalities	232	46.1	111	121
Anoxia (asphyxia)	67	13.3	9	58
Nonsyphilitic infections	66	13.1	17	49
Hemorrhage, traumatic	65	12.9	15	50
Malformations	49	9.7	3	46
Miscellaneous	18	3.6	0	18
Syphilis	3	0.6	0	3
Blood dyscrasia	3	0.6	0	3
	503	100.0	155	348

* The infant is placed in the previable or the premature group in this classification if at least two of the following criteria are present: previable: length, 28.0 to 34.9 cm.; weight, 400 to 999 Gm.; gestation, 22 through 28 weeks; premature: length, 35.0 to 46.9 cm.; weight, 1,000 to 2,499 Gm.; gestation, 29 through 38 weeks. (From Dunham,[3] p. 48.)

effect of the degree of immaturity which we are unable to measure and record and do the best we can in carefully comparing mortality figures for different weight groups. We should consider the cause of the premature delivery and whether

a baby was transported far from one institution to another or from a home to a hospital. We must avoid including infants admitted to an institution because of some special difficulties. Different lying-in hospitals have different criteria for admissions, and one will have a far greater proportion of difficult deliveries than will another. The fact that 78 per cent of all babies were delivered in hospitals in the United States in 1943, which is 24 per cent higher than in 1938, may mean that mortality and morbidity figures can be evaluated more correctly in the future.

Prognosis for Growth and Development.—The uncertainty of prognosis derives, in part, from the profound ignorance of the basic causes of prematurity. Although certain crude factors are understood, such as the effects of hemorrhage, diarrhea and hypothermia, on an infant's chance for survival, there is no way of evaluating the innate vitality and urge to grow of the germ plasm itself.

A. The prognosis for life depends on

1. Type of birth and immediate medical care. This includes the type of delivery (if a breech, there is more likelihood of intracranial injury and death than with vertex delivery), whether the baby had attendance by a physician or midwife, whether the baby was born at home and had undue exposure to cold.

2. The degree of immaturity of the infant at birth and the extent of anatomic and physiological deviations from normal newborn infants.

TABLE 6.—*Prognosis for Survival* *

Weight Group (Gm.)	Per Cent Survival	Prognosis
2,001 to 2,500	At least 93	Excellent
1,501 to 2,000	At least 82	Good
1,000 to 1,500	At least 50	Fair

* From Dunham,[2] p. 83.

3. The type of congenital malformations present, if any.

4. The medical care during the neonatal period or until the premature infant has made its own physiological adjustments to its environment, with emphasis on

(*a*) Prevention of infection.

(*b*) Control of environment.

(*c*) Special technics of feeding and types of formulas.

Table 6 reveals the prognosis for survival under good conditions of care.

B. The prognosis for future development (physical, mental and emotional) depends on

1. Physical development. It is evident that there is a great difference in growth between premature infants and infants who have spent the full gestational period within the uterus. We can often tell from the appearance of some babies 4 or 5 months old, or even of children 2 and 3 years old, that they were born prematurely. This difference in appearance may even be permanent. The appearance is particularly notable in those babies with low birth weights, as in those weighing under 3 pounds. It is evident that the character of the extra uterine growth differs qualitatively from that of the growth the infant would have had if it had remained the last month or two in the uterus, and this difference

occurs even though the rate of growth may be such that the infant quickly catches up with its brother in weight.

Ylppö (1919)[6] reported on repeatedly obtained weights and measurements of 700 premature infants. He concluded that, with some exceptions, premature infants with a birth weight of 2,500 Gm. or less showed a tremendous disturbance in growth during the first three to five years of life. The weight and length remained lower during this period than in a comparable age group of full term children. The smaller the weight and length at birth, the greater was the delay in growth. The disturbance in growth was proportionally greatest between the sixth and twelfth months of life. Between 2 and 4 years the premature infants began to catch up to the normal children and most of them did so by the age of 5 or 6 years. From this time on their weight and length curves corresponded with those of full term children, except for the smallest premature infants (weighing less than 1,000 Gm.). Retardation in the growth of the thorax lasted about three years, and growth of head was least retarded. Ylppö attributed some of this disturbance of growth to undernutrition and secondarily to infection, as well as unsatisfactory function of endocrine glands and inertness of movement.

We can at present only speculate about the nature of the physiological deviations which cause this difference in the quality of growth. This evident difference may well be on some endocrine basis and not caused by nutrition, in its narrow sense. It is possible, for instance, that in the last month of intrauterine life the fetus may be influenced by the high level of estrogen which occurs in the mother's body. The prematurely born baby may escape this influence or, perhaps we should say be denied it. The absence of this stimulus is held by several authors, on a basis of speculation rather than of evidence, to be partly responsible for the drowsiness and generally depressed condition of metabolism (the major handicap of the young premature baby). According to the advocates of this theory, the administration of estrogens remedies the deficiency and thereby enables the premature infant to gain weight and improve its state generally in a more satisfactory way than the untreated infant. The main impression gained from a review of studies relating to this matter is that the results reported[7] are poorly controlled and too much emphasis is laid on relatively slight evidence that babies treated with estrogens made better progress than untreated babies.

2. Mental and emotional development. The importance of prematurity as a cause of death must be weighed in the light of knowledge of the prognosis of prematurity regarding other features than life and death. How important is it to keep premature babies alive except to make a better survival curve? What sort of adult persons do premature infants make? There have been at least 75 studies of the intellectual prognosis of premature infants, 71 of which were reviewed by Benton.[8] None of them seems to offer both decisive and dependable answers to our questions.

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6. Ylppö, A.: Pathologisch-anatomische Studien bie Frühgeborenen, Ztschr. f. Kinderh. **20**:212, 1919.

7. Moncrieff, A.: Value of Oestrin for Premature Babies, Arch. Dis. Childhood **11**:9, 1936.

8. Benton, A. L.: Mental Development of Prematurely Born Children, Am. J. Orthopsychiat. **10**:719, 1940.

Probably the studies of Mohr and Bartelme [9] give the best evaluation of prognosis in terms of socioeconomic status of families. They used standard objective test scales, instead of the usual subjective criteria, with a fairly accurate control group and rather critical evaluation of the results.

Of the total group of 250 premature infants, 124 were compared with their 152 full term siblings. All had a slightly inferior socioeconomic status. They were evaluated with the Gesell, Stanford-Binet and Kuhlmann-Binet tests, with the following results:

(*a*) No difference was observed in the mental growth between healthy, prematurely born infants and their siblings if allowance was made for the degree of prematurity. The correction for the months of prematurity was particularly important for the first two years of life, up to which time they showed definite retardation. Compared with their siblings, the prematurely born infants demonstrated significant retardation in walking alone; the mean age for the use of single words was 18 months, and speech difficulties, particularly stammering, were more frequent than in their full term siblings.

(*b*) Prematurely born infants more frequently had temper tantrums and were dependent on their mothers, whereas full term infants were more adequate in their early social responses and had better relations with their siblings and children outside the home.

(*c*) There was no relationship between weight at birth and intelligence in children of mothers who had toxemia, renal complications and syphilis.

(*d*) "Mental-test ratings for the prematurely born children classified according to type of delivery [showed that] delivery by Caesarean section apparently tends to decrease frequency of injuries during the birth process as compared with results noted after breech delivery and extraction . . . although [not] from a statistical standpoint." [9]

Of the total group of 250 premature infants there were 69 that showed definite intracranial hemorrhage at birth (an incidence of 27.6 per cent), and 22 had a definite tendency to be retarded (an incidence of 31.9 per cent). Physical examination indicated that among these 22 children who were mentally below average 20.3 per cent had evidence of motor lesion. Mohr and Bartelme summarized this work by saying that they had evidence which confirmed "the statement that the intracranial hemorrhage cases showing neurological lesions are a most important factor in contributing to the differences in the mental-growth curve of the total prematurely born group and that of the full-term children."

The mental growth curves for the prematurely born children who are not given a diagnosis of intracranial hemorrhage at birth and those for siblings and standardization groups reveal that there is no definable difference in the mental growth curves of these groups. "This observation further substantiates the conclusion that the mental development of prematurely born children, except for those injured at birth, differs in neither rate nor amount from the development of full-term children." [9]

9. Mohr, G. J., and Bartelme, P. F.: Developmental Studies of Prematurely Born Children, in Hess, J. H.; Mohr, G. J., and Bartelme, P. F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, University of Chicago Press, 1934, pp. 57-217.

The obvious objections to this study are that (1) the authors did not know how the diagnosis of intracranial hemorrhage at birth was made in some cases and that (2) they stated that the development of the premature infant is as good as that of its full term sibling if intracranial hemorrhage has not occurred. Intracranial hemorrhage is one of the greatest hazards of being born prematurely. In the compilation of statistics one should not compare a total group of full term infants with a partial group of premature infants from whom all abnormal infants have been excluded. Total groups must be compared.

In summary, the present evidence indicates that group for group, regardless of immediate etiological factors, premature infants have a higher incidence of mental deficiency than do full term infants. The need for further investigation in this field is apparent. The factors that lead to mental deficiency are not necessarily inherent in prematurity but may be as preventable as is brain injury in the full term infant.

TABLE 7.—*Causes of Prematurity*[10]

	Per Cent
1. Unknown	30.7 to 64.7
2. Disturbances in maternal health	8.7 to 63.6
a. Toxemia of mother	
b. Systemic infection of mother	
c. Nutrition of mother	
d. Age of mother	
3. Multiple births	6.3 to 22.9
4. Obstetric complications	5.5 to 60.9
a. Disturbances in uterus and birth canal	
Premature rupture of membranes	
Placenta previa	
Premature separation of placenta	
Bleeding, cause unknown	
Hydramnios, etc.	
b. Genital tract abnormalities	
5. Deformity of the fetus	
6. Trauma due to coitus in 3d trimester of pregnancy	

Causes and Prevention of Premature Birth.—In table 7 a simple classification of causes of prematurity is presented, with figures adapted from a review of the literature by Anderson and Lyon.[10]

The table gives the lowest and highest incidence of varying causes of prematurity as recorded by 13 American authors. It indicates again that we do not know the cause of prematurity in the majority of cases. The order of frequency listed in the table is not statistically significant because of the tremendous variation in causes reported by different workers.

The responsibility for the prevention of prematurity belongs to the internists and obstetricians, and complete reports are given elsewhere.

It is important to note that the role of a good maternal diet during pregnancy is assuming more importance in the light of several recent studies.[11] A diet high in protein, minerals and vitamins results in a more viable, larger baby than the

10. Anderson, N. A., and Lyon, R. A.: Causes of Prematurity: I. Review of the Literature, Am. J. Dis. Child. **58**:586 (Sept.) 1939.

11. (*a*) Tyson, R. M.: A 15-Year Study of Prematurity from the Standpoint of Incidence, Mortality, and Survival, J. Pediat. **26**:648, 1946. (*b*) Ebbs, J. H.; Tisdall, F. F., and Scott, W. A.: The Influence of Prenatal Diet on the Mother and Child, J. Nutrition **22**:515, 1941. (*c*) Burke, B. S.; Harding, V. V.; Kirkwood, S. B., and Stuart, H. C.: Nutrition Studies During Pregnancy, Am. J. Obst. & Gynec. **46**:38, 1943.

unsupervised diet. The incidence of miscarriages, stillbirths and premature births is reduced on this regimen.[11b] The incidence of toxemia, often listed as a cause of premature birth, is definitely reduced.[11c]

RESPIRATION

The next two sections are devoted indirectly to the medical care of premature babies. The medical care depends on a knowledge of (1) the anatomic and physiological deviations from normal and the methods of correction, (2) the nutritional requirements of premature infants and (3) the prevention and treatment of infection.

The anatomic and physiological deviations are classified according to systems only for convenience of reference, but the reader is reminded that the subjects thus presented are usually interrelated. Thus, the sections on respiration and renal function must be read and understood together and not as though dealing with separate systems.

Explanations for Respiratory Failure.—On consideration of the causes of death in prematurely born infants, it is obvious that, although there may be manifold physiological deficiencies to explain the failure of these babies to cope successfully with their new environment, the faulty action of respiration is usually the most evident sign of such failure and apparently the immediate cause of death. Gross disturbances in respiration are frequently evident in both healthy and sick premature infants.

We may consider three explanations for the respiratory failure of premature infants who are free from infection or congenital anomalies:

1. An injury associated with the trauma of birth to the centers responsible for the nervous control of respiration, abnormal chemical stimuli to these centers or a failure of development of these centers may have occurred. Dysfunction of the centers of the brain stem controlling respiration due to inadequate development or mechanical or asphyxial injury is highly probable in many cases. The irregularity of breathing and the intermittent nature of the cyanotic attacks point to a central neurological disturbance which sometimes becomes apparent at autopsy.

2. The ineffective action of feeble respiratory muscles on a poorly developed thoracic cage is seen during inspiration, when it can often be observed that the diaphragm contracts vigorously but results only in causing the thoracic wall to be greatly retracted along the line of attachment of the diaphragm. The total volume of the thoracic cavity seems little increased by such inspiration, the descent of the diaphragm being offset by the contraction of the thorax, so that a surprisingly small amount of air can be heard entering the lungs for the magnitude of the effort required.

3. The state usually diagnosed as "atelectasis" may be considered when the lung (*a*) either is not capable of expansion (*b*) or is anatomically perfect and expansible but has not expanded for some physiological reason. The first type is seen extensively in premature infants in whom masses of undeveloped cells without alveolar structure are present.[12] Here we do not see atelectasis in the usual sense of the word but as simply masses of fetal cells no more capable of

12. Farber, S., and Wilson, J. L.: Atelectasis of New-Born: Study and Critical Review, Am. J. Dis. Child. **46**:572 (Sept.) 1933.

being expanded by inspiration than any other organ of the body. The second and commonly recognized type of atelectasis is found to some extent in all newborn infants and persists for many days. This type of atelectasis is commonly diagnosed and offered as the explanation of attacks of cyanosis in full term, as well as premature, infants. It is frequently given as the cause of death, because this type of atelectasis is itself the result of one of two factors—the obstruction of the passage of air to the air sacs by plugging of the bronchioles in some manner or the insufficient expansion of the thoracic cavity, due to weakness or to a disturbed central control of respiration. This is secondary atelectasis and no satisfactory explanation in itself for respiratory failure.

Points 1, 2 and 3 *a* are anatomic causes for respiratory failure, but point 3 *b* indicates a physiological deviation from normal in premature infants.

Periodic respiration is commonly seen in premature infants and may be another indication of the basic pathological mechanism that leads at times to the persistence of atelectasis. The usual concept of periodic breathing is as follows: The irregular respirations result from low metabolism and oxygen utilization. An increase in tissue and, in turn, of blood lactic acid then occurs. The blood lactic acid combines with sodium, with the subsequent release of bicarbonate, which in turn causes an increase in free carbon dioxide, which stimulates the respiratory

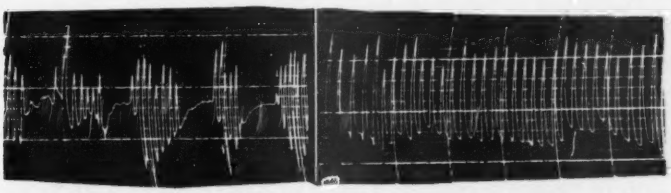

Fig. 4.—Plethysmographic recording of respiration in a normal premature infant. Left, record of breathing in atmosphere; right, record on administration of oxygen. (From the Laboratory of the Department of Pediatrics, University of Michigan Medical School.)

centers, and a relative hyperpnea ensues. When this carbon dioxide is blown off, the blood again becomes more alkaline, and again apnea is induced. Thus, a cycle of periodic hyperpnea and apnea occurs.

Do premature infants suffer from "hypoxia"? We know that the administration of air of high oxygen content will change the irregular respiration of premature infants to regular respiration [12] (fig. 4).

In addition, relative measurements of tidal volume, rate and minute volume before and after the administration of oxygen all indicate that alveolar ventilation may be improved with the administration of oxygen.[13b] One could reasonably assume, therefore, that a state of relative oxygen deficiency does exist. This has been explained as due to one or to a combination of the following causes:

1. Subnormal pulmonary ventilation. In adults the low oxygen tension of high altitudes will cause similar respiration.

13. (*a*) Wilson, J. L.; Long, S. B., and Howard, P. J.: Respiration of Premature Infants: Response to Variations of Oxygen and to Increased Carbon Dioxide in Inspired Air, Am. J. Dis. Child. **63**:1080 (June) 1942. (*b*) Graham, B. D.; Reardon, H. S.; Wilson, J. L.; Tsao, M., and Baumann, M. L.: Physiologic and Chemical Response of Premature Infants to Oxygen-Enriched Atmosphere, Pediatrics **6**:55, 1950.

2. An impediment to the exchange of oxygen between the lungs and the blood. It is known that in premature infants the interstitial tissue of alveoli is considerably thicker than in full term babies, and that there is a greater distance through which gases must diffuse from the alveolar spaces to the blood.

3. The inability of blood to give up oxygen due to a different type of hemoglobin (a fetal hemoglobin) or a decrease in the volume flow of the capillary blood. However, since arterial oxygen saturation studies [13b] on premature infants (table 8) have been shown to be within normal adult limits, it is apparent that the pulmonary ventilation, even though inefficient, is adequate to saturate their hemoglobin.

That the anoxia of premature infants is a tissue anoxia is not proved but seems probable. This relative tissue anoxia may be due to the fact that the reaction of the hemoglobin of premature infants in respect to oxygen exchange is similar to the reaction of the hemoglobin of the fetus in utero, i. e., hemoglobin takes on oxygen more readily in the alveoli at a low oxygen tension but gives it up less readily to the tissues than does the adult type hemoglobin.

In any event, the use of oxygen is justified in all small premature infants at birth and in all premature infants who are not doing well during their neonatal course.

TABLE 8.—*Arterial Blood Studies* *

	Premature Infants (62)	Adult Controls (12)
p_H	7.31	7.41
CO_2 content, mEq./L.	20.5	24.4
CO_2 tension, mm. Hg	38.7	37.4
Arterial oxygen saturation, %	92	94

* From the Laboratory of the Department of Pediatrics, University of Michigan Medical School.

Carbonic Anhydrase.—Another cause of respiratory difficulties in premature infants is said to be low blood levels of carbonic anhydrase. Carbonic anhydrase is an enzyme which is carried in the red blood cells and acts to increase the conversion of bicarbonate to carbon dioxide. Meldrum and Roughton [14] demonstrated in goat fetuses that the level of carbonic anhydrase does not begin to rise until very near term. Stevenson [15] studied the amount in premature babies, and, although no precise relationship between the birth weight and the level of the enzyme could be demonstrated, small premature infants of 1,500 Gm. or less tended to show the lowest level of the enzyme (one-fourth that of adults). Low levels in premature infants are entirely compatible with life, but he stated that premature infants may not have clinical symptoms because of their relative inactivity. However, with increased activity, such as after feeding or exertion or during infections, the frequency of cyanotic attacks suggests that the level in premature infants is not adequate. Stevenson gave several theoretical reasons why a low blood level of carbonic anhydrase might interfere with oxygenation of the blood:

1. Oxygenation of hemoglobin is physiologically speeded when the blood gives up carbon dioxide in the lungs.

14. Meldrum, N. U., and Roughton, F. J. W.: Carbonic Anhydrase: Its Preparation and Properties, J. Physiol. **80**:113, 1933.

15. Stevenson, S. S.: Carbonic Anhydrase in Newborn Infants, J. Clin. Investigation **22**:403, 1943.

2. The hemoglobin dissociation curve is shifted to the left in proportion to the lowering of carbon dioxide tension.

He stated that it is possible that a low blood level of carbonic anhydrase delays the lowering of the carbon dioxide tension in the lung capillaries, resulting in a small and incomplete oxygenation of hemoglobin. However, we know (see table 8) that the majority of premature babies have a low plasma carbon dioxide content, a low p_H and, by calculation, a normal carbon dioxide tension in the alveoli of the lungs.[16] We know, too, that oxygen saturation of arterial blood is almost normal in the majority of premature infants, but that when premature infants are given more oxygen we have evidence that they profit from it. Day and du Pan [17] have gone further with this study and have shown "that, though the blood level (in 31 cases) of carbonic anhydrase is indeed low in premature infants, there is no correlation of its level with oxygen saturation or carbon dioxide content." Although carbonic anhydrase of the red blood cells in premature infants is low, at present there is no proof that the amount of the enzyme present is not adequate.

RENAL FUNCTION

The study of normal renal function in infancy is being actively pursued by many investigators. In the immediate future we should have more complete information to add to our understanding of the physiological peculiarities of all infants and, thus, to aid in their treatment in disease. The most detailed review describing the anatomy, cellular chemistry and physiology of infants' kidneys has been written by McCance,[18] and the reader is referred to this article. At present the majority of work has been done on full term infants, and abnormalities thus disclosed will be only relatively true for premature infants. These studies should be repeated on premature infants, since anatomic and physiological deviations are so much greater in premature than in full term infants. For example, as many observers [19] agree, the function of the kidney in premature infants as compared with full term infants is modified by the fact that glomeruli are still developing in infants with a birth weight under 5 to 5½ pounds (2,268 to 2,494 Gm.).

In utero the regulation of the internal environment of animals is carried on by the placenta, although the kidneys begin to form and secrete urine before birth,[20] perhaps as early as the second or third month of fetal life.[21] A few minutes after birth the kidneys take over the work of the placenta.

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16. Reardon, H. S.; Graham, B. D.; Wilson, J. L.; Baumann, M. L.; Tsao, M., and Murayama, M.: Studies of Acid Base Equilibrium in Premature Infants, Pediatrics **6**:753, 1950.

17. Day, R., and du Pan, R. M.: Carbonic Anhydrase in Blood and Kidneys of Premature Infants, in Transactions of Society for Pediatric Research, 1947, Am. J. Dis. Child. **77**:109 (Jan.) 1949.

18. McCance, R. A.: Renal Function in Early Life, Physiol. Rev. **28**:331, 1948.

19. Eckhardt, C. T.: Ueber die compensatorische Hypertrophie und das physiologische Wachsthum der Niere, Virchows Arch. f. path. Anat. **114**:217, 1888. Potter, E. L., and Thierstein, S. T.: Glomerular Development in Kidney as an Index of Fetal Maturity, J. Pediat. **22**:695, 1943.

20. Hewer, E. E., and Keene, M. F. L.: Foetal Development, J. Obst. & Gynaec. Brit. Emp. **30**:345, 1923. Needham, J.: Chemical Embryology, London, England, Cambridge University Press, 1931.

21. Cameron, G., and Chambers, R.: Direct Evidence of Function in Kidney of Early Human Fetus, Am. J. Physiol. **123**:482, 1938.

Chemical Composition of the Blood.—It has long been noted that the majority of premature infants have an acidosis, manifested by a low p_H and low carbon dioxide values.[22] Table 9 reveals the hydrogen ion concentration found in a study of 92 premature infants. Recent work [16] has shown that other constituents of extracellular fluid in well premature infants differ from normal and points to the need for further investigation. Table 10 reveals that total base, chloride, phosphate and "R" [23] are all increased and carbon dioxide content, protein and p_H are all decreased in the blood of premature infants as compared with adults.

We know that premature babies contain more water per pound of body weight than do full term infants. It is conceded that they contain more extracellular fluid per pound of body weight, as confirmed by a comparison of thiocyanate space and radiosodium space in infants and adults.[23a] All published analyses have shown that newborn animals and fetuses contain more sodium and chloride per pound of body weight than do adults. We know that premature infants have less plasma protein than adults, particularly less plasma albumin than globulin.[24] Thus, the colloidal osmotic pressure of the serum is lower and favors an accumulation of fluid in the tissue spaces and an increased filtration rate in the kidneys. The

TABLE 9.—*Average Hydrogen Ion Concentration: Total Carbon Dioxide Content and Carbon Dioxide Tension in Arterial Blood of Ninety-Two Premature Infants* [16]

Premature Infants			Total CO_2 Content, mEq./L.	pCO_2, mm. Hg (Calculated)	Comment
No.	%	p_H			
61	67	7.29	19.2	37.8	Metabolic acidosis*
12	13	7.38	23.9	39.2	Normal*
10	10	7.25	23.7	51.1	Respiratory acidosis*
6	7	7.43	19.9	29.6	Respiratory alkalosis*
3	3	....	....	....	Unclassified*

* Chemical, not clinical, impression.

latter is apparently modified by the increased percentage of sodium and chloride in premature infants.

Urine Volumes and Osmotic Pressure.—Although the premature infant is able to concentrate urine to the point where the osmotic pressure in the urine is greater

22. (*a*) Ylppö,[6] p. 214. (*b*) Räihä, C. E.: Säuglingsmortalität und Frühgeburtlichkeit, Acta pædiat. **28**:27, 1940. (*c*) Marples, E., and Lippard, V. W.: Acid-Base Balance of New-Born Infants: II. Consideration of the Low Alkaline Reserve of Normal New-Born Infants, Am. J. Dis. Child. **44**:31 (July) 1932. (*d*) Branning, W. S.: Acid-Base Balance of Premature Infants, J. Clin. Investigation **21**:101, 1942. (*e*) Wilson, J. L.; Reardon, H. S.; Murayma, M.; Graham, B. D.; Tsao, M. V., and Baumann, M. L.: Anaerobic Metabolism in the Newborn Infant: I. On the Resistance of the Fetus and Newborn to Oxygen Lack, Pediatrics **1**:581, 1948.

23. "R" represents the acid constituents of the blood not analyzed in the study and includes sulfate, organic acids and phosphate (in those infants in whom phosphate was not analyzed). "R" was calculated by subtracting the sum of the acid fractions from the total base of the blood.

23a. Flexner, L. B.; Wilde, W. S.; Proctor, N. K.; Cowie, D. B.; Vosburgh, G. J., and Hellman, L. M.: Estimation of Extracellular and Total Body Water in Newborn Human Infants with Radioactive Sodium and Deuterium Oxide, J. Pediat. **30**:413, 1947.

24. McMurray, L. G.; Roe, J. H., and Sweet, L. K.: Plasma Protein Studies on Normal Newborn and Premature Infants: I. Plasma Protein Values for Normal Full Term and Normal Premature Infants; II. Use of Concentrated Normal Human Serum Albumin in Treatment of Premature Infants, Am. J. Dis. Child. **75**:265 (March) 1948.

than in the plasma,[25] under the same conditions of water deprivation adults would concentrate much more. Premature infants do not appear to have polyuria, in spite of the difficulty in concentration. This phenomenon has not been fully explained to date.

The urinary output and concentration in the first week of life for a group of normal premature infants are given in table 11.

Excretion of Water.—It has been shown [26] that full term babies under 3 months of age excrete less urine than infants over 3 months and that infants under 6 months

TABLE 10.—*Acid-Base Equilibrium of Arterial Blood in Premature Infants and Adult Controls* [22e]

	No. of Determinations		p_H	CO_2 Content, mEq./L.	pCO_2, mm. Hg	Cl, mEq./L.	Protein, mEq./L.	PO_4, mEq./L.	Total Base, mEq./L.	B, mEq./L.
Premature infants	73	Average	7.31	20.1	38.0	111	12.7	4.1 (13)*	159	15 (60)*
		Range	7.18	10.9	21.5	99	10.0	3.7	152	11 (13)*
			7.48	29.1	58.0	124	15.7	4.8	171	..
Adults	13	Average	7.41	24.4	37.4	102	17.0	2.01	154	11
		Range	7.38	23.1	35.0	98	15.7	1.77	152	..
			7.44	26.4	42.5	105	17.4	2.58	156	..

* Adult inorganic phosphorus of plasma calculated on the basis of an assumed p_H of 7.40. Numbers in parentheses indicate number of determinations.

TABLE 11.—*Urine Volume and Osmotic Pressure* *

Infant	Birth Weight, Gm.	Edema	Thirsting and Fasting, Hr.	Highest Temperature, C.	Weight Loss, %	Urine Volume, Ml./Sq. M./Hr.	Maximal Urine Concentration, Milliosmoles/L.
1	2,106	0	54	36.7	4.1	5.9	400
2	1,648	0	57	36.9	7.2	8.6	618
3	1,530	?	52.5	38.3	8.2	6.9	536
4	1,625	?	75.5	36.5	12.3	6.2	570
5	1,956	+	60	36.7	10.0	7.4	468
6	2,265	++	72	36.7	13.0	11.4	510
7	1,685	++	69	36.5	17.5	12.5	478
8	2,210	++	112	36.2	20.0	6.3	578
9	2,260	+++	74.5	36.1	15.5	17.5	527
10	1,655	+++	69	36.5	19.0	12.6	624
			Fasting only, hr.				
11	2,238	0	72	36.9	7.5	22.4	218
12	1,970	++	72	37.2	5.8	22.8	338

* From Smith, C. A., and others: Pediatrics 3: 34, 1949.

excrete less than those over 6 months. So far it has not been shown that administration of posterior pituitary hormone leads to a decreased excretion of water.[27] This work needs to be repeated.

25. Smith, C. A.: Renal Function in Early Post-Natal Life in Premature and Mature Infants, in the Proceedings of the Fifth International Congress of Pediatrics. New York, 1947. Thomson, J.: Observations on Urine of New Born Infant, Arch. Dis. Childhood **19**:169, 1944.

26. Lasch, W.: Weiteres über den Wasserversuch im Säuglingsalter, Ztschr. f. Kinderh. **36**:42, 1923. Aschenheim, E.: Der Wasserversuch bei Säuglingen, ibid. **24**:281, 1920.

27. Heller, H.: Renal Function of Newborn Infants, J. Physiol. **102**:429, 1944.

Fluid Requirements.—The fluid requirements of premature babies have been carefully studied by Gordon and Levine.[28] They have shown that premature babies receiving an average of about 2 ounces of water per pound, or 135 cc. per kilogram, of body weight lose less water through the skin and lungs than do full term babies. This might be expected because the heat production is low, the sweating mechanism is not fully developed and heat is lost more easily by radiation and convection than in full term babies. On this intake premature babies retain adequate amounts of water for health, with a surplus for excretion in the urine. Furthermore, increasing the fluid intake above the minimum amount necessary for water retention will only increase the amount excreted in the urine. On the other hand, decreasing the fluid intake from 170 to 130 cc. per kilogram of body weight does not lower the water loss through feces, skin and lungs but rather causes a pronounced decrease in the urinary output. The authors find, though, that reducing the intake below 74 to 85 cc. per kilogram, or 1½ ounces per pound, produces a negative water balance, with development of fever. Therefore, it seems necessary to feed babies between 2 and 3 ounces of fluid per pound, or 125 to 150 cc. per kilogram, of body weight.

Osmotic Diuresis.—Dean and McCance [29] have shown that if a 10 per cent solution of sodium chloride or a 20 per cent solution of urea is given in the dose of 5 per cent of the body weight to newborn infants, a diuresis of small magnitude is obtained, and the osmotic pressure of urine may rise slightly or remain unchanged. The percentage of the dose of sodium chloride excreted in infants is much less than in adults. The absence of diuresis means that newborn infants are incapable of doing much to restore their internal environment to normal.[29]

Glomerular Function.—It has been shown by Barnett [30] and McCance and Young [31] that the glomerular filtration rate in newborn infants, as manifested by inulin clearance, is less than half the value found in adults, and the glomerular filtration rate varies with the hydration of the baby. Further studies of sick infants with dehydration are obviously necessary.

Urea Clearance.—Urea clearance varies with the degree of hydration of the infant, as shown by two independent groups of workers.[32] Urea clearances in newborn infants under 14 days of life are far below those of adults, when compared on the basis of surface area. Young and McCance have shown [33] that they approach adult levels toward the end of the first year of life.

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28. Gordon, H. H., and Levine, S. Z.: The Metabolic Basis for the Individual Feeding of Infants, Premature and Full-Term, J. Pediat. **25**:464, 1944.

29. Dean, R. F. A., and McCance, R. A.: Inulin, Diodone, Creatinine and Urea Clearances in Newborn Infants, J. Physiol. **106**:431, 1947.

30. Barnett, H. L.: Renal Physiology in Infants and Children: Method for Estimation of Glomerular Filtration Rate, Proc. Soc. Exper. Biol. & Med. **44**:654, 1940.

31. McCance, R. A., and Young, W. F.: Secretion of Urine by Newborn Infants, J. Physiol. **99**:265, 1941.

32. (*a*) Young, W. F.; Hallum, J. L., and McCance, R. A.: The Secretion of Urine by Premature Infants, Arch. Dis. Childhood **16**:243, 1941. (*b*) Barnett, H. L.; McNamara, H.; Hare, R. S., and Hare, K.: Influence of Postnatal Age on Kidney Function of Premature Infants, Proc. Soc. Exper. Biol. & Med. **69**:55, 1948.

33. Young, W. F., and McCance, R. A.: Secretion of Urine by Dehydrated and Normal Infants, Arch. Dis. Childhood **17**:65, 1942.

Tubular Function.—Although glomeruli excrete creatinine, diodone [32b] and paraaminohippuric acid,[34] their excretion is usually considered to be a manifestation of tubular function. Since it has been shown that the tubules of newborn infants cannot completely excrete diodone, creatinine or paraaminohippuric acid, it is assumed that tubular function in newborn infants is not as efficient as it will be in later life.

Mineral Clearances.—The clearance of a threshold substance, such as glucose, chloride and sodium, depends on (*a*) the glomerular filtration rate, (*b*) minute volume, (*c*) concentration in the serum and (*d*) the reabsorbing activity of the tubules, which, in turn is partially controlled by the cortex of the adrenal gland and posterior lobe of the pituitary. Young, Hallum and McCance [32a] reported that the chloride clearances were low in all infants and much lower in premature than in full term infants. In infants of all ages the chloride clearance tends to fall as the volume of urine per minute decreases. The potassium clearance also varies with the minute volume. It is not known whether this is due to decreased glomerular filtration rate or increased reabsorption by the tubules. Phosphate clearance varies directly with the minute volume and is less in full term infants under 14 days of age than in adults.

Titratable Acidity.[18]—The titratable acidity and the ammonia nitrogen of the urine rise and fall with the total nitrogen (that is, the concentration of the urine). Therefore, they are determined by the age of the infant and are highest between the fifth and seventy-second hours of life. The titratable acids are an assortment of weak organic acids, such as uric acid, lactic acid and beta-hydroxybutyric acid, and phosphates. The phosphates are usually spoken of as the main buffer acids in the urine. Of the total acid excreted by the kidney uncombined with fixed base, a higher proportion tends to be combined with ammonia in infancy than in adult life and a smaller proportion tends to be found as free titratable acid. The explanation for this lies in the excretion of phosphates. Phosphates do not stimulate the kidney to excrete ammonia, but they may contribute greatly toward the magnitude of the titratable acidity. The urine in infants may contain practically no phosphates. The direct comparison between the urinary phosphate of infants and of adults is made by considering the ratio of phosphate to nitrogen. This eliminates the difference between the adult and the infant urine when dilution is a factor. The ratio of phosphate to nitrogen for infant urines is 2.92 and for adult urines 12.64. This suggests that serum phosphorus clearances are likely to be much lower in infants than in adults. Therefore, the proportion of the titratable acidity due to phosphates is much lower in infants than in adults, and the proportion due to organic acids is much higher. The small amount of phosphate available for excretion in infancy may limit materially the amount of free acid which the kidneys can excrete, and this no doubt explains, in part at any rate, why the ammonia coefficients are so high. In the absence of buffer substances in the urine there would naturally be a tendency for acid substances to be excreted in combination with ammonia.

34. West, J. R.; Smith, H. W., and Chasis, H.: Methods of Measuring Renal Clearance with Special Reference to Infancy and Childhood, in the Proceedings of the Fifth International Congress of Pediatrics, New York, 1947.

In the ammonia coefficients, the ratio of ammonia to titratable acid and the ratio of phosphate to nitrogen, and in the percentage of the titratable acidity due to organic acids, the urine of the newborn infants has been found to resemble that of adults in ketosis.

Comment.—Renal function cannot be interpreted without considering the internal environment and respiration. The increase in total base and chloride in the blood may well be due to increased tubular reabsorption of premature kidneys.[32a] With an increase in the "R" fraction of the blood above "normal," partly due to phosphate and partly presumably due to organic acids, there is certainly an increased need for conservation of base. The elevated chloride of blood is not entirely explained by the decrease in carbon dioxide content of blood, although that is undoubtedly the predominating factor. The recent work of Gordon and his associates [35] revealed that the administration of ammonium chloride to three premature babies was followed by the excretion of a high average percentage (98 per cent) of the ingested dose, which seems to indicate that kidneys can clear chloride if necessary.

The increased hydrogen ion concentration of well premature infants is not explained by the present knowledge of renal function. Present evidence suggests that the chronic acidosis of premature infants is due to anoxia, which in turn causes an increase in tissue organic acids, presumably lactic and pyruvic acids.[22e] Certain renal function studies [36] imply that this is true, as there is a relative increase of organic acids in the urine. Evidence supporting the concept of chronic anoxia has been presented by Wilson and co-workers [22e] (see section on "Respiration"). Thus, we believe that acidosis and anoxia in premature infants are associated with a partial anaerobic metabolism for a variable period after birth, which depends on the degree of immaturity.

What are some of the clinical implications of these findings? We know that there can be no rigid rules for therapy with the present lack of complete knowledge of the intracellular and extracellular fluid metabolism of premature infants. Administration of sodium lactate has been recommended [37] as therapy for infants who are found to have acidosis. Studies have shown that the majority of infants have a metabolic acidosis and that a small percentage have respiratory acidosis, but the majority do well clinically. It seems neither practical nor logical to carry out the long term of therapy which would be necessary to correct this type of acidosis. In addition, due to the fact that lactate is excreted almost unchanged by the urine in premature infants,[37] the need of extra base for the excretion almost negates the theoretical value of this type of therapy.

However, studies which show a high hydrogen ion concentration and the tremendous limitations of the kidneys in their capacity to handle the work required suggest that premature infants have no chemical margin of safety. When they have any stress, such as infection, vomiting, improper feeding or diarrhea, they can rapidly progress, in a matter of hours, to a severe acidosis which needs prompt

35. Gordon, H. H.; McNamara, H., and Benjamin, H. R.: The Response of Young Infants to Ingestion of Ammonium Chloride, Pediatrics **2**:290, 1948.

36. Branning.[22d] Räihä, C. E.: Ueber einige Neugeborenenprobleme (vorläufige Mitteilung), Acta pædiat. **28**:390, 1941.

37. Dunham.[8] McBryde, A., and Branning, W. S.: Spontaneous Acidosis in Premature Infants: A Clinical Report, J. Pediat. **20**:549, 1942.

alleviation, or death ensues. The nature and extent of the acidosis must be determined by chemical sampling, with careful clinical interpretation of the patient. Although our knowledge of the amount of intracellular and extracellular water in premature infants is far from complete, we do know that the ability to concentrate urine by the kidneys is less adequate than in adults under the same conditions and that an early and severe loss of fluid in ill premature infants must be alleviated. We do not know the optimal type or quantity of repair solutions for the severely ill premature infants. At present, sodium bicarbonate has theoretical advantages over sodium lactate for reasons just mentioned. Sodium chloride and dextrose solutions are time-honored remedies.

REGULATION OF BODY TEMPERATURE

The inability of the premature infant to maintain his own body temperature at a constant and usual level is well known.[38] This thermolabile state is, of course, only one result of the complex factors of immaturity, and it can be partly explained by an inadequate vasomotor control, inability to sweat and lack of the usual insulation of subcutaneous fat, combined with the relatively large surface area. When a premature and a full term infant are placed naked side by side in a room which gradually is allowed to become colder, the changes in skin temperature which are known to take place as a protective reaction, do not occur in the premature as they do in the larger infant. The temperature at which shivering begins, for instance, is lower in the premature infant, or else he does not shiver at all. Therefore, the premature infant loses an excessive amount of body heat, and his body temperature falls. Fear of these low temperatures and the harm they may do almost dominate discussion on care of the premature infant. It is less commonly recognized that a premature infant's temperature will rise above a normal level with as little provocation as it will fall below that level. An environment slightly too warm, due to an overheated incubator or to the ill advised use of hot water bottles, will raise a baby's temperature abnormally as easily as chilling will depress it (fig. 5).

To have a properly and automatically regulated environment is of great aid.[38a] A baby whose body temperature fluctuates around 97 F. seems statistically to be in better condition than one whose temperature is fluctuating around 99 or 100 F. There is a great tendency, however, to keep babies too warm. In general, we can say that a constant body temperature in an infant is safer than an irregular temperature and that a temperature somewhat lower than the traditional "normal" is better than one somewhat higher.

Figure 6 illustrates the correlation between gradual rise in temperature and gain in weight as an infant matures. The infants in this study were in an air-conditioned nursery, and no great efforts were made to keep the babies' temperature at a "normal" level. In one of them, and this has been seen in many infants doing

38. (*a*) Blackfan, K. D., and Yaglou, C. P.: The Premature Infant: A Study of the Effects of Atmospheric Conditions on Growth and on Development, Am. J. Dis. Child. **46**: 1175 (Nov., pt. 2) 1933. (*b*) Day, R.; Curtis, J., and Kelly, M.: Respiratory Metabolism in Infancy and in Childhood: XXVII. Regulation of Body Temperature of Premature Infants, ibid. **65**:376 (March) 1943. (*c*) Day, R., and Hardy, J. D.: Respiratory Metabolism in Infancy and in Childhood: XXVI. A Calorimeter for Measuring the Heat Loss of Premature Infants, ibid. **63**:1086 (June) 1942.

quite satisfactorily, it was almost 28 days before the temperature spontaneously reached 98 F. We feel this type of care is far safer than that in which the incubator forces the infants' temperature to "normal," since resulting fluctuations

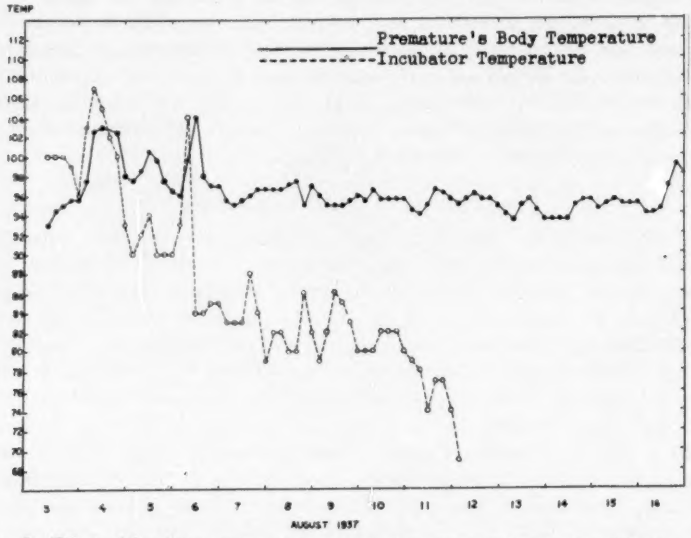

Fig. 5.—Effect of incubator temperature on body temperature of premature infants. Solid line indicates premature infant's body temperature and broken line the incubator temperature.

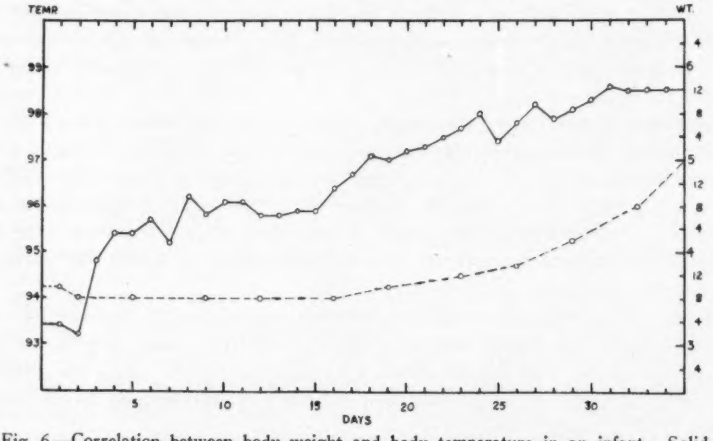

Fig. 6.—Correlation between body weight and body temperature in an infant. Solid line indicates body temperature and broken line body weight. (From Wilson, J. L.: Unpublished data.)

are wide, and often temperatures of 101 F. or greater are reached. It will usually be found that the baby's temperature at the higher levels fluctuates more than at the lower levels. A lower temperature of the environment can be compensated

for to a certain extent by higher humidity, but the opposite is not true; that is, a low humidity and a high environmental temperature, such as 25 per cent relative humidity and a temperature of 95 F. are dangerous. Humidities between 50 and 60 per cent are best for most premature infants, but in this respect there is an interesting point not often enough described. As babies get larger, they do not do well in these high humidities. Starting at a weight of a little above 4 pounds (1,800 Gm.), many premature infants will lose their appetite, have a fluctuating temperature and show signs of indigestion, if kept for long in an environment with a humidity of 60 per cent. It is usually a good plan to have babies removed from that environment at least by the time they have reached a weight of 5 pounds, and it is believed that most babies at this weight will do better at home than in a hospital.

CARDIOVASCULAR SYSTEM

Blood Volume, Cardiac Output and Heart Size.—The blood volume at birth is estimated to be about 10 per cent of the body weight, and the cardiac output is well over 500 cc. per minute, which is considerably larger than the adult output in proportion to body weight. The heart is relatively large at birth, with a right ventricular preponderance which lasts for several months as indicated by the electrocardiogram. Therefore, in any roentgen examination of the chest of the newborn infant in terms of cardiac size, it is difficult to be sure whether the infant has an actual or simply a relative cardiac enlargement.

Blood Pressure and Pulse Rate.—Accurate measurements of the blood pressure in premature infants are difficult to obtain, but in general it can be said that the systolic blood pressures are between 60 and 80 mm. of mercury. The pulse rate of all newborn infants varies tremendously during the first few weeks of life. The normal pulse rate in premature infants can be considered as somewhere between 90 and 180 beats per minute.

Vascular Fragility.—Vascular fragility is apparent to anyone who has tried to inject anything into a premature infant's veins, as well as from the clinical evidence of increased susceptibility to being bruised and the gross evidence of hemorrhage. Various experimental studies have proved this to be true. We also know that the number of capillaries per unit of tissue in the liver and brain in premature infants depends on their intrauterine age and that, in general, there is a smaller capillary bed than in the full term infant.

Prothrombin Level.—The prothrombin level in premature infants, like that of full term infants, changes soon after birth. This is a controversial subject, but it is generally believed that premature infants have hypoprothrombinemia or a more labile prothrombin level. Poncher and Kato [39] found no correlation between birth weight and prothrombin time during the first 11 days of life. Because of the variability of the prothrombin level in premature infants, studies suggest that vitamin K should be given to all premature infants, and particularly to their mothers before delivery. Administration of vitamin K will not solve all the bleeding difficulties to which these babies are subject, since it will not correct hepatic deficiency or capillary fragility. The effective dose of vitamin K has not been estab-

39. Poncher, H., and Kato, K.: Treatment of Hypoprothrombinemia Haemorrhagica Neonatorum (Hemorrhagic Disease of Newborn) with Vitamin K, J. A. M. A. **115**:14 (July 6) 1940.

lished for premature infants. The customary dose is 2 mg., which is about twice the known effective dose for full term infants.[40]

Hemopoietic System and Iron Metabolism.—The range of normal values for hemoglobin content and red and white blood cell counts in premature infants is great, primarily because of the varying degrees of immaturity among premature babies. We do know that the average red blood cell count (5,500,000), hemoglobin concentration (22 Gm.) and white blood cell count (7,500) of premature infants at birth are slightly lower than the values for full term infants.[41] The average levels for hemoglobin and hematocrit for the first five weeks of life as shown in table 12 (compiled in this department) differ from other reported data, probably because of the method. It is interesting to note that, although the hematocrit during the first week is 1.8 times greater than in the fifth week, the hemoglobin fall is less rapid, with a comparable difference between the first and fifth week of 1.5 times.

The color index of the newborn premature baby is over 1, with a gradual fall to the third month, when it reaches unity. After the third month, the color index

TABLE 12.—*Hematocrit and Hemoglobin Values at Various Ages in Premature Infants*

Age, Wk.	No. Determinations	Hematocrit, %	Age, Wk.	No. Determinations	Hemoglobin Concentration, Gm.*
1	31	51	1	24	16.2
2	13	48	2	10	16.2
3	17	42	3	16	14.8
4	6	35	4	5	11.8
5+	19	29	5	4	11.0
..	..	..	6+	9	9.8

* Hemoglobin determination by Van Slyke oxygen capacity method. Unpublished data from the Pediatric Department, University Hospital, Ann Arbor, Mich.

becomes less than 1. The reticulocyte count is high at birth, with a value of 5 to 10 per cent.[42] The reticulocytes fall rapidly until the tenth day, when they almost disappear. Josephs [42b] noted that they gradually reappear the third week and reach their highest value at 6 to 12 weeks, when the hemoglobin concentration is at its lowest level. Merritt and Davidson [41] stated that the reticulocyte count remained relatively low throughout the first year of life.

Thrombocytes (platelets), as reported by Merritt and Davidson,[41] are low at birth, with an average value of 192,000. They increase steadily to the sixth month, to a value of 304,000, and thereafter remain relatively stable.

There is a large proportion of immature white cells of all forms in the circulating blood at birth which remains for many weeks. Thus, from a practical standpoint, the white blood cell count and differential count in premature infants as a measure of infection are often unsatisfactory.

40. Hardwick, S. H.: Studies in Minimal Effective Dose of Water-Soluble Vitamin K Substitute in Prevention of Hypoprothrombinemia in Newborn Infant, J. Pediat. **24**:259, 1944.

41. Merritt, K. K., and Davidson, L. T.: The Blood During the First Year of Life: Anemia of Prematurity, Am. J. Dis. Child. **47**:261 (Feb.) 1934.

42. (*a*) Merritt and Davidson.[41] (*b*) Josephs, H. W.: Anemia of Prematurity, Am. J. Dis. Child. **48**:1237 (Dec.) 1934.

Although the red blood cell count, hemoglobin concentration and hematocrit are relatively high at birth, they fall rapidly, so that by 2 to 3 weeks of age premature infants have an anemia in which blood values usually reach the lowest level at 6 weeks to 3 months of age and do not return spontaneously to normal until 6 to 7 months of age. This seems to occur regardless of iron, liver or copper supply. Premature infants have a curious defect in iron metabolism in that the administration of iron prophylactically will not prevent the occurrence of this iron deficiency anemia or immediately correct it in the early period of the anemia. However, after a delayed response, iron administration shortens the duration of anemia. Josephs [42b] demonstrated that curves for hemoglobin content and red blood cell count for untreated patients of less than 1,700 Gm. in weight tend to reach lower levels than those for infants over 1,700 Gm. in weight; the average lowest points for hemoglobin concentration are 7.5 and 8.3 Gm., respectively. Blackfan and Diamond [43] showed that the average low value for red blood cell count is 2,500,000 at 3 months of age in premature infants. Neither group of infants

TABLE 13.—*Average Hemoglobin Levels from Six to Ten Weeks of Age* [42b]

	Untreated Infants Hb., Gm.	Infants Given Iron Before 30th Day Hb., Gm.
Patients over 1,700 Gm.	8.3	10.0
Patients under 1,700 Gm.	7.5	8.5

TABLE 14.—*Response to Iron Therapy (Time Needed for Rise in Hemoglobin Levels) Given Before Thirty Days of Age* [42b]

	Untreated Infants, Time Required, Days	Treated Infants, Time Required, Days
Patients over 1,700 Gm.	0 to 100	40 to 50
Patients under 1,700 Gm.	0 to 100	50 to 90

displayed a spontaneous tendency for the hemoglobin content or red blood cell count to rise during the first 100 days of life. Blackfan and Diamond [43] have noted that a spontaneous return to normal starts in the fourth month of life and is completed by the seventh to eighth month in well premature infants.

Josephs stated that when a 10 per cent solution of ferric ammonium citrate, in a dose of 2 cc. per kilogram of body weight per day, is given early (10 to 30 days of age) to premature babies (table 13) the spontaneous decrease in hemoglobin noted in untreated patients occurs, but there are two differences: 1. The hemoglobin curve and red blood cell count do not reach as low levels. 2. About the fortieth to fiftieth day for the patient over 1,700 Gm. and somewhat later (58 to 90 days) for those under 1,700 Gm. (table 14), there occurs a general rise in hemoglobin level. This work is not accepted by all observers.

Premature babies treated with iron after the fortieth day showed a sharp rise in hemoglobin and reticulocyte response. In general, the lower the hemoglobin level when iron therapy takes effect, the sharper the rise will be.

43. Blackfan, K. D., and Diamond, L. K.: Atlas of the Blood in Children, New York, Commonwealth Fund, 1944.

As a result of these observations two periods in the development of physiological anemia in premature infants may be considered: (1) the early period characterized by a rapidly falling hemoglobin content and red cell count with a failure of response to treatment with iron and (2) a later period in which the hemoglobin content and red blood cell count of untreated babies remain at a low figure but respond well to iron therapy.

Although we know that the iron content in the body of the premature infant is inadequate to prevent evidence of hypochromic anemia, it is evident that the giving of iron preparations will not completely prevent a drop in hemoglobin levels but will accelerate the recovery from the anemia after a latent period of six to 10 weeks. The fact that the bone marrow puts out reticulocytes throughout the greater part of the time from the birth of the baby up to and including the time the hemoglobin value reaches its lowest point (6 to 10 weeks of age) indicates that the low hemoglobin content and red cell count are not due to hypoplasia of the bone marrow in a strict anatomic sense.[42b] The anemia of prematurity is probably due to a combination of the following factors:

1. Hemoglobin and red cell formation and iron storage are lacking for the period of intrauterine existence of which the premature infants were deprived.

2. The persistence of fetal hemoglobin for a long time after birth may interfere with new hemoglobin formation.

3. The rapid growth of premature infants implies a tremendous need for iron beyond the amount available.

SKELETAL SYSTEM

Calcium and Phosphorus Metabolism.—It is evident there is a tremendous defect in calcium metabolism in a premature baby, primarily due to the fact that less calcium is laid down in the bones before birth than in the full term infant. Stearns,[44] in an analysis of the calcium content of fetuses, reveals that the relative, as well as absolute, body percentage of calcium increases steadily throughout the fetal periods. At birth the body of a normal baby weighing 3,000 Gm. contains 20 to 25 Gm. of calcium, or approximately 8 Gm. per kilogram of body weight.

In a study [45] of the calcium and phosphorus metabolism of premature infants compared with full term infants given cow's milk supplemented with vitamin D, it has been shown that premature infants are able to retain calcium and phosphorus from cow's milk in proportionately greater amounts than do full term infants.

It is evident from table 16 that human milk has proportionately less calcium and phosphorus than does cow's milk. However, the calcium to phosphorus ratio is 2.3 in human milk, as compared with 1.3 in cow's milk. The optimum calcium to phosphorus ratio in infancy is thought to be about 2.

With reference again to table 15, less than 50 per cent of calcium present in human milk is retained by premature infants, as compared with an average of 71 per cent retention from cow's milk. The fact that the retention ratio of calcium to phosphorus in premature infants fed human milk is much lower than in those

44. Stearns, G.: The Mineral Metabolism of Normal Infants, Physiol. Rev. **19**:415, 1939.

45. Benjamin, H. R.; Gordon, H. H., and Marples, E.: Calcium and Phosphorus Requirements of Premature Infants, Am. J. Dis. Child. **65**:412 (March) 1943. Daniels, A. L.; Stearns, G., and Hutton, M. K.: Calcium and Phosphorus Metabolism in Artificially Fed Infants: Influence of Cod Liver Oil and Irradiated Milk, ibid. **37**:296 (Feb.) 1929.

fed cow's milk is interesting in the light of the original proportion of calcium and phosphorus offered in cow's milk versus human milk. At present, there is no explanation for this phenomenon.

Thus, the evidence indicates that premature babies do obtain and retain more calcium and phosphorus from cow's milk supplemented with vitamin D than from human milk supplemented with vitamin D. Owing to increased rate of growth and lack of calcium and phosphorus stores in premature infants, it seems logical to use the milk from which the minerals not only are well utilized but are provided in greater amounts.

TABLE 15.—*Average Calcium and Phosphorus Retention of Young Infants* [45]

		Calcium				Phosphorus			
			Retention				Retention		Retention Ratio (Ca:P)
Type of Infant	Type of Milk*	Intake, Mg./Kg.	Mg./Kg.	% of Intake	Gm./Kg. Wt. Gain	Intake, Mg./Kg.	Mg./Kg.	% of Intake	
Premature	Human	56	27	45 (33 to 51)	1.9	28	24	87 (84 to 91)	1.1
Premature	Cow	165	114	71 (55 to 80)	9.4	109	63	61 (51 to 70)	1.8
Full term	Cow	179	56	31 (13 to 46)	8.9	139	35	26 (16 to 31)	1.5

* Supplemented by vitamin D.

TABLE 16.—*Percentage Composition of Cow's Milk and Woman's Milk*

Constituents	Woman's Milk, %		Cow's Milk, %	
Protein:				
Lactalbumin	0.75		0.50	
Casein	0.50	1.25	3.00	3.50
Sugar (lactose)		7.50		4.75
Fat		3.50		3.50
Minerals:				
Sodium	0.011		0.061	
Potassium	0.048		0.154	
Calcium	0.034		0.122	
Magnesium	0.005		0.013	
Chloride	0.036		0.116	
Phosphorus	0.015		0.060	
		0.20		0.75
Water		87.55		87.50
Total		100.00		100.00

In spite of the increased calcium content of the skeleton in infants fed cow's milk and vitamin D, premature infants often show deviation from the normal bone pattern at the epiphysial junction. The deviations appear to be similar to those observed in infants not given vitamin D, except that in the latter group such irregularities seem to precede clinical rickets, whereas in the group retaining more calcium these irregularities are transitory. They appear during the period of most rapid growth and disappear without change in dietary regimen. This fact has led to much confusion in the literature regarding rickets. In fact, it is almost impossible to prevent a rapidly growing premature infant from showing some of the minimal roentgenographic signs of rickets, which probably are not of clinical significance. These changes are apparently due to the tremendous rate at which calcium needs to be laid down. The changes associated with rickets may also be

related to the excretion of calcium and phosphorus, as well as to the phosphatase activity in the bone. Premature infants have chronic mild acidosis and low phosphaturia (see section on "Renal Function"). We know that in adults a diversion of calcium to the urine results from acidosis and a lack of phosphaturia. We know, too, that a relatively high tissue p_H (7.4) is necessary for optimal phosphatase activity, and that premature infants tend to have a low plasma p_H average of 7.3. Both these factors may influence the rate at which new bone is laid down and may be particularly important during the period of most rapid growth, when there is a greater need for calcium and phosphorus than can be met by the available supply.

GASTROINTESTINAL SYSTEM

Liver Function.—We have certain evidence that liver function in premature infants is different from that in full term babies. The liver has a multitude of

TABLE 17.—*Fasting Blood Sugar Values* *

	Full Term	Premature
Number of infants	17	20
Number of determinations	28	40
Blood sugar average (1st 48 hr.)	49.9 mg.	31.8 mg.

* From Miller, H. C., and Ross, R. A.: J. Pediat. 16: 473, 1940.

TABLE 18.—*Four Hour Fasting Blood Sugar Values of Premature Infants* *

Blood sugar, mg./100 cc.	0 to 30	30 to 35	35 to 45	45 to 50	50 to 55	55 to 60	60 to 65	65 to 70	70+
Number in each group	2	2	3	10	6	10	17	14	34

	Age Distribution						
	0 to 7 Days	7 to 14 Days	2 to 3 Wk.	3 to 7 Wk.	1 to 2 Mo.	2 to 3 Mo.	3 to 4 Mo.
Number over 70 mg.	5	6	4	7	12	5	1
Number 60 to 70 mg.	7	6	4	8	6	2	2
Number under 60 mg.	21	4	2	2	4	0	0

* From van Creveld, S.: Am. J. Dis. Child. 38: 912 (Nov.) 1929.

duties, and we must admit that it is inaccurate and vague to speak of liver function as though it were a single measurable activity. Much of the prothrombin deficiency in the premature infant, as well as in full term newborn babies, is due mainly to "liver function deficiency" rather than to lack of vitamin K. Hypoproteinemia, hypoglycemia and icterus neonatorum of newborn premature infants may be hepatogenic.

Hypoglycemia.—Blood sugar values in premature infants at birth tend to be lower than those in full term infants, as shown in table 17. Inadequate glycogen stores plus relative starvation may account for the low blood sugar values during the first week of life. They do not account for persistence of a low blood sugar level after feedings are well established. This work should be repeated with the type of feedings for premature infants (high protein, high carbohydrate diets) which are commonly used in this country. Recent work on animals [46] suggests

46. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

that anoxemia accelerates glycogenolysis, which may be a factor in the variable blood sugar values found in premature infants.

The total plasma proteins are considerably lower in premature than in full term infants. Recent work [24] indicates that the albumin and globulin fractions of full term infants are within the normal adult range of 4.5 to 6.5 Gm. per 100 cc. for albumin and 1.2 to 2.2 Gm. per 100 cc. for globulin. However, in premature infants, the globulin fraction is within normal limits, while the albumin fraction is low.

Serial determinations on a group of small premature infants showed a wide range, with erratic fluctuations of the albumin and total protein contents of the plasma, there being no significant increase with increasing age and development of the infants.[24]

Because of the low plasma albumin, concentrated (25 Gm. per 100 cc.) normal serum albumin was given to a group of premature infants. A steady increase in the albumin and total protein content of the plasma, with lower values for plasma

TABLE 19.—*Values for Plasma Protein for Seventy-Eight Newborn Infants During the First Week of Life* [24]

Weight of Infants at Birth	Albumin			Globulin			Total Protein		
	No. of Determinations	Mean Value, Gm./100 Cc.	Standard Deviation	No. of Determinations	Mean Value, Gm./100 Cc.	Standard Deviation	No. of Determinations	Mean Value, Gm./100 Cc.	Standard Deviation
3 lb. 8 oz. to 3 lb. 15 oz.	12	4.7*	0.55	12	1.45	0.45	13	5.57	0.58
4 lb. to 4 lb. 7 oz.	19	4.2	0.57	18	1.67	0.29	22	5.5	0.41
5 lb. to 5 lb. 7 oz.	6	4.3	0.33	6	1.66	0.46	6	5.8	0.44
Total premature infants	37	4.3†	0.60	36	1.69	0.57	41	5.6†	0.47
5 lb. 8 oz. to 6 lb. 7 oz.	15	4.7	0.55	17	1.69	0.55	16	6.3	0.66
6 lb. 8 oz. to 7 lb. 7 oz.	17	4.7	0.59	18	1.88	0.44	18	6.4	0.74
7 lb. 8 oz. to 8 lb. 7 oz.	14	4.8	0.39	15	1.67	0.54	16	6.4	0.41
Total full term infants	46	4.8†	0.47	50	1.75	0.49	50	6.4†	0.60

* The values for albumin for these small infants probably are not reliable, as it was extremely difficult to secure clear, nonhemolyzed serum from them.

† The differences between the mean values for albumin and for total protein are significantly higher for full term infants than for premature infants when tested by the method of t. For total protein, $t = 6.5$; for albumin, $t = 4.0$.

globulin, resulted. These workers [24] agree that the infants made a more rapid gain in weight and had fewer illnesses than the infants who received no albumin. They believe that the optimum results were obtained on the infants who received 3 cc. per pound (0.5 Kg.) of body weight with injections twice a week for three or four weeks, depending on the albumin content of the plasma.

In a previous study, Sweet and others [47] gave 2.5 cc. of serum gamma globulin to 117 premature infants on the second, eighth and fifteenth hospital days and thereafter every two weeks until they reached the weight of 5½ pounds. They observed that (1) there was no difference in mortality rate as compared to untreated infants; (2) there was no difference in morbidity, and (3) the average time to regain birth and discharge weight was slightly less than for the infants who were treated with gamma globulin, but the differences were so slight that they could not be regarded as significant.

47. Sweet, L. K., and others: Use of Normal Serum Gamma Globulin Antibodies (Human) Concentrated (Immune Serum Globulin) in Treatment of Premature Infants, J. Pediat. **28:** 571, 1946.

Whatever the relation may be to plasma protein, the observation that premature infants have little immunity to infection is well established. We cannot overestimate the importance of this lack of immunity to pathogenic organisms. We must consider a premature infant as an open Petri dish filled with culture medium ready to grow any bacteria that falls on it. Infection is the greatest danger that any premature infant faces, outside of the immediate risk of being born. It is not an exaggeration to state that a 2 pound (907 Gm.) premature infant with a "cold" is as dangerously ill as a 2 year old child with peritonitis. Before the days of chemotherapy the "cold" in a 3 pound infant almost inevitably progressed to pneumonia and death. We are not quite sure how much immunity we can furnish passively to these babies, but the possibility provides some logical basis for the use of transfusions of adult blood and/or gamma globulin.

Prolonged physiological jaundice occurs in practically all premature infants as compared with an incidence of approximately 50 per cent [48] in the full term infants. The hyperbilirubinemia cannot entirely be accounted for by the increased destruction of red blood cells after birth. We know, too, that an abnormal amount of bilirubin is present in the blood of full term infants at birth.[49] Schick [50] has demonstrated a higher icterus index in the umbilical cord blood of premature infants than in that of full term babies.

Several theories have been advanced to account for hyperbilirubinemia at birth. In premature infants the evidence seems to point to deficiency in liver function. Ylppö [51] and others [52] found that there is a relationship between the development of jaundice and the amount of bilirubin in the meconium at birth, suggesting the inability of the liver to excrete bile. Ross and his associates [53]

found that although large amounts of urobilin, as well as of bilirubin and biliverdin, were present in the stools during the first week of life—the average total was somewhat less in the icteric than in the nonicteric infants. This is contrary to what one might expect in a purely hemolytic type of jaundice. Since in the presence of a normally functioning liver increased blood destruction is accompanied by an increased urobilinuria,[54] the findings in these infants suggests a failure of normal hepatic action.

Food Requirements.—Table 20 shows the daily caloric requirements for premature and full term babies, broken down for certain fractions. One can see that in terms of metabolism per unit of body weight the premature baby's "basal" metabolism is slightly greater than that of the full term baby. When referred to surface area, the basal metabolism of premature infants is less than that of full

48. Smith, C. A.: The Physiology of the Newborn Infant, Springfield, Ill., Charles C Thomas, Publisher, 1945.

49. Davidson, L. T.; Merritt, K. K., and Weech, A. A.: Hyperbilirubinemia in Newborn, Am. J. Dis. Child. **61**:958 (May) 1941.

50. Schick, B.; Weiner, S. B., and Reiner, M.: Icterus Index of Cord Blood: Genesis of Icterus Neonatorum, Am. J. Dis. Child. **64**:655 (Oct.) 1942.

51. Ylppö, A.: Icterus neonatorum und Gallenfarbstoffsekretion beim Foetus und Neugeborenen, Ztschr. f. Kinderh. **9**:208, 1913.

52. Nakamura, H., cited by Reuss, A.: Physiologie des Früh- und Neugeborenen und Säuglings, natürliche Ernährung, Monatsschr. f. Kinderh. **72**:402, 1938. Schwartz, P.: Zur Frage des Icterus neonatorum, Ztschr. f. klin. Med. **100**:117, 1924.

53. Ross, S. G.; Waugh, T. R., and Malloy, H. T.: Metabolism and Excretion of Bile Pigment in Icterus Neonatorum, J. Pediat. **11**:397, 1937.

54. Elman, R., and McMaster, P. D.: Relation Between Urobilin and Conditions Involving Increased Red Cell Destruction, J. Exper. Med. **42**:619, 1925.

term infants, a finding common to small animals in which the body surface is greater in relation to the total mass so that more heat is radiated. However, this slightly increased basal metabolism is more than offset by the fact that the premature baby sleeps more and is less active when awake. The premature baby moves and cries in 24 hours far less than its full term brother (tables 20 and 21). On the other hand, the increment of increase in weight is greater. The premature infant grows faster. It has to accumulate more per unit of original weight in building more muscles, more fat and more bones if it is to catch up with its full term brother, so that the caloric need per pound of body weight for that purpose is a little larger.

The premature baby makes less efficient use of its food than the full term infant does. It absorbs less fat and excretes much more fat in the stool; because of this

TABLE 20.—*Average Daily Caloric Requirements* *

	Premature Infants		Full Term Infants†	
	Calories/Kg.	Calories/Lb.	Calories/Kg.	Calories/Lb.
Basal	60‡	27	55§	25
Specific dynamic action	5 } = 10	2 } = 4	7	3
Activity	5 }	2 }	17	8
Fecal loss	20	9	10	5
Growth	30	14	20	9
Total	120	54	109	50

* From Gordon, H. H., and Levine, S. Z.: Am. J. Dis. Child. 52: 810 (Oct.) 1936 and Holt and Howland.[56]
† Eight weeks of age.
‡ 58 in first week.
§ 46 in first week.

TABLE 21.—*Twenty-Four Hour Energy Exchange* *

	Distribution of Time/24 Hr.	
	Premature %	Full Term %
Sleep	61	50
Crying†	7	3
Feeding	7	3
Wakefulness (without crying)	25	44
	100	100

* From Gordon, H. H., and others: Am. J. Dis. Child. 59: 1185 (June) 1940.
† Crying practically doubles metabolism (90 per cent), whereas wakefulness without crying causes only 15 per cent rise in metabolism.

waste, the requirements of total food intake must be made a little greater. If, therefore, we balance these factors against each other, the increased basal metabolism, the increased fecal loss and the increased growth against the diminished activity, we find that the food requirements of full term and premature babies, expressed in calories per pound of body weight, are surprisingly similar.

Fat: In addition to the fact that fecal caloric loss is higher in premature than in full term infants, Gordon and McNamara [55] found that, in studies using human milk and cow's milk mixtures in which olive oil replaced the butter fat, qualitative alterations in the dietary fat had no effect on the heightened fecal loss of fat.

55. Gordon, H. H., and McNamara, H.: Fat Excretion of Premature Infants: Effect on Fecal Fat of Decreasing Fat Intake, Am. J. Dis. Child. **62**:328 (Aug.) 1941.

Quantitative reduction of dietary fat, however, consistently led to diminished excretion of fecal fat. Approximately doubling fat intake doubles fat excretion in stools and halves the weight gain. Whatever the cause of this defect, it does not arise from a failure of digestive enzymes to split fat in the bowel.[56]

Protein: In contrast to this defective absorption of fat, the capacity of premature infants to absorb and retain nitrogen is highly efficient. Premature infants absorb the nitrogen from cow's milk at least as well as that from human milk, and raising the protein intake from 2.8 to 4.7 Gm., or even higher, does not lower the coefficient of digestibility, approximately 90 per cent being absorbed at each level of intake.[57] This percentage is well within the normal range of nitrogen absorption of adults. Not only do premature infants have no difficulty in absorption but with higher intake of nitrogen they retain more in their bodies per unit of weight than do full term infants. The evidence suggests that the heightened retention of nitrogen in young infants is related to their increased rate of growth.[57] Therefore, 4 to 5 Gm. of protein per kilogram of body weight per day is utilized by premature babies.

TABLE 22.—*Gain in Weight During First Month of Life in Premature Infants* [58]

	Wt., 1,900 to 2,000 Gm.				Wt., 1,300 to 1,400 Gm.			
	Fed on Breast Milk Alone		Fed on Breast Milk Plus Aminosol*		Fed on Breast Milk Alone		Fed on Breast Milk Plus "Aminosol"*	
Age	Cases	Average Weight, Gm.	Cases	Average Weight, Gm.	Cases	Average Weight, Gm.	Cases	Average Weight, Gm.
Birth	38	1,961	9	1,962	30	1,368	7	1,354
1 wk	37	1,813	9	1,900	29	1,249	7	1,376
2 wk	38	1,925	8	2,079	28	1,354	7	1,521
3 wk	36	2,036	6	2,223	23	1,505	6	1,697
1 mo	25	2,226	6	2,523	21	1,697	6	2,008
Gain in weight during first month of life, Gm.	..	265	..	561	..	329	..	654

* "Aminosol" contains 25 per cent amino acid mixture, 25 per cent dextrose and 1.5 per cent salt mixture.

Human milk supplies 1.2 per cent protein. Cow's milk contains 3.5 per cent. One way to obtain the necessary protein intake in premature infants is to use cow's milk and reduce its fat content.

One group of workers [58] has supplemented breast milk with a mixture of amino acids and dextrose (80 to 85 per cent free amino acids) prepared from casein by hydrolysis. This dosage was equivalent to 2.5 Gm. of amino acids per kilogram of body weight except "during the earliest days." The study was controlled by giving the babies breast milk one week and breast milk supplemented with this mixture of amino acids and dextrose the next; the weight gains were then compared. The weight gain was consistently greater in the group receiving supplemented breast milk.

56. Levine, S. Z., and Gordon, H. H.: Physiologic Handicaps of the Premature Infant: I. Their Pathogenesis, Am. J. Dis. Child. **64**:274 (Aug.) 1942.

57. Gordon, H. H.: Prematurity, in Levine, S. Z., and others: Advances in Pediatrics, 1947, New York, Interscience Publishers, Inc., vol. 2, pp. 315-345.

58. Jorpes, E.; Magnusson, J. H., and Wretlind, A.: Casein Hydrolysate: Supplementary Food for Premature Infants, Lancet **2**:228, 1946.

Another recent study [59] indicates that protein milk is harmful for premature infants. "Studies of electrolyte balance and serum analyses made on 3 premature infants showed that a diet of unmodified powdered protein milk for three days produces a serious acidosis with elevated serum chloride and lowered serum bicarbonate levels." However, it should be noted that this product was made by precipitation of casein with calcium chloride and the addition of casein to whole milk, according to a method recommended by Finkelstein. The mixture was then evaporated to a powder. These results, therefore, may be only the effect of the administration of an excess of calcium chloride in the protein milk mixture. The increased urinary output which resulted may also have been due to calcium chloride diuresis. Therefore, the electrolyte balance studies in this series might be considerably influenced by the calcium chloride content of the milk mixture.

Carbohydrate: Levine and Gordon [60] have shown the ease with which carbohydrate is utilized by premature babies. Under 9 days of age premature babies had respiratory quotients between 0.77 and 0.95. This was precisely the range for full term babies from the age of 1 to 12 months. Premature babies more than 9 days old had a slightly different respiratory quotient, varying between 0.87 and 0.95. This indicates that carbohydrate utilization is similar in premature and full term babies and is very efficient.

Vitamins A and D: In premature babies observed to have poor retention of fat, absorption of vitamin A was also poor, whereas infants who retained fat well absorbed vitamin A efficiently. In a group of 89 premature infants studied by Henley and co-workers,[61] plasma vitamin A levels were found to be significantly higher in the infants who received vitamin A from the third day of life than in those not given extra vitamin A. About one fourth of the premature infants not given supplementary vitamin A had levels below the usually accepted minimum value. Also, in the study of livers obtained at autopsy from premature and full term infants who died within one day of birth of causes not thought to have affected the vitamin A deposition, it was found that without exception mature infants' livers contained higher stores of vitamin A than the livers of premature babies. The average amount in percentage was more than twice as great, and the amount in the entire liver was more than five times as great in full term as in premature infants. Because they are likely to absorb both fat and vitamin A less efficiently than full term babies do and because premature infants who do not receive supplements of vitamin A have low levels in the blood plasma, early supplementation of diets for premature infants with concentrates containing vitamin A seems a desirable routine.

Recent work by another group [62] on use of 2.0 to 3.0 cc. of synthetic vitamin A in an alcohol or propylene glycol vehicle indicates but inconclusively that mixtures of synthetic vitamins A and D are more desirable than the fat-soluble

59. Hoffman, W. S.; Parmelee, A. H., and Grossman, A.: Mechanism of Production of Acidosis in Premature Infants by Protein Milk, Am. J. Dis. Child. **75**:637 (May) 1948.

60. Levine, S. Z., and Gordon, H. H.: Physiologic Handicaps of the Premature Infant: II. Clinical Applications, Am. J. Dis. Child. **64**:297 (Aug.) 1942.

61. Henley, T. F.; Dann, M., and Golden, W. R. C.: Reserves, Absorption and Plasma Levels of Vitamin A in Premature Infants, Am. J. Dis. Child. **68**:257 (Oct.) 1944.

62. Clifford, S. H., and Weller, K. F.: Absorption of Vitamin A in Prematurely Born Infants, Pediatrics **1**:505, 1948.

preparations. Ninety per cent of the group receiving the former had good absorption levels, whereas only 7 per cent of the group given the latter had good levels. However, other studies [63] indicate that (1) there is a tremendous variation within individual persons in time of absorption and (2) with oily preparations the highest levels are attained about one hour later than with synthetic preparations. Through the taking of only one sample instead of repeated samples, both these observations were ignored. This study should be repeated. Nevertheless, on theoretical evidence use of the synthetic preparations is desirable in premature infants because of both (*a*) the lack of fat in the preparation and (*b*) the proportionally high amount of vitamin A in the synthetic preparations as compared with the oil preparations.[64]

We also know that premature infants are susceptible to rickets (as discussed in the section on "Calcium and Phosphorus Metabolism"). There is need for administration of larger amounts of vitamin D orally in premature babies for at least two reasons: (1) the rapid rate of growth and (2) the excessive loss of fat-soluble vitamin in the stool of those premature infants who have a defect in fat absorption. Therefore, it seems advisable that at least twice as much vitamin D should be used in the feeding of premature infants as for full term infants.

Vitamin C: When premature infants were fed cow's milk mixtures of high protein content,[65] 1-p-hydroxyphenyllactic and p-hydroxyphenylpyruvic acids appeared in the urine in significant amounts as early as the sixth day of life and persisted as long as vitamin C administration was withheld. These abnormal products are not present in the urine of full term infants, but they can sometimes be produced by giving a single large dose of either tyrosine or phenylalanine and can be abolished by the administration of 100 to 500 mg. of ascorbic acid. The significance of this excretion of the abnormal products of protein metabolism is unknown; however, on these theoretical grounds, when premature babies are given cow's milk, particularly with a high protein content, they should also be given appreciable amounts of vitamin C, despite the fact that they do not show clinical evidence of scurvy.

Vitamin B: There is no direct knowledge concerning the amount of vitamin B necessary for the feeding of premature or full term infants. With the present limitation of knowledge, the vitamin B content is presumed to be adequate in human and cow's milk.[66]

SUMMARY OF PRINCIPLES OF CARE

The principal purpose of this section is not to offer a detailed discussion of treatment but rather a short summary of the principles of care derived from present knowledge of physiology.

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63. Weick, G., and Tsao, M. U.: Comparison of Vitamin A Absorption in Normal Children and Children with Cystic Fibrosis of the Pancreas Using Oily and Water Soluble Preparations, Univ. Hosp. Bull., Ann Arbor **13**:114, 1947.

64. There is some evidence, as yet unconvincing, that the administration of relatively large amounts of vitamin A to a premature infant may be responsible for the condition of retrolental fibrodysplasia.

65. Levine and Gordon.[55] Levine, S. Z.; Dann, M., and Marples, E.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants, J. Clin. Investigation **22**: 551, 1943.

66. Holt, L. E., and Howland, J.: Holt's Diseases of Infancy and Childhood, revised by L. E. Holt Jr., and R. McIntosh, ed. 11, New York, D. Appleton-Century Company, Inc., 1940.

A discussion of proper care can logically be divided into four categories:

1. Protection of the premature infant from infection.
2. Proper nutrition and good nursing and medical care.
3. Control of environment—maintenance of temperature and proper humidity.
4. Diagnosis and treatment of illness.

The four items are arranged in this order to emphasize their relative importance, though, of course, neglect of any one may result in a premature infant's death. Nevertheless, protecting the baby from the slightest infection is most important, and, except for deaths due to the immediate difficulties of delivery, it is fair to say that most premature infant's deaths are due to an acquired infection.

With all the rules and regulations which we may devise for care of premature babies, one point cannot be overemphasized. Nothing satisfactory can be done without a good nurse. One can hardly exaggerate the importance of a nurse who is so used to premature infants that she can tell from the way the baby wrinkles its nose or the color around its lips whether it is feeling as well today as it was yesterday, whether the food it is getting should be reduced in amount or increased. She can detect the early signs of disease or "indigestion" before it appears clear-cut on the chart from vomiting, diarrhea or irregular temperatures.

Protection from Infection.—As we have already pointed out, although the premature infant is highly susceptible to infection, its early reaction to infection is nonspecific, and only by subtle signs can the initiation of infection be recognized. The customary technics that have been evolved for the protection of the premature infant require little discussion. The need for scrubbing of the hands and wearing of gowns is well recognized. If masks are worn, they should be properly made of well washed, porous muslin of at least three layers and should be of the moose face type, that is, with a large space enclosed by the mask in front of the nose and mouth. It should be changed at least three times a day. It should never be put on again after once being used. Most of all, we should recognize that the wearing of a mask does not justify a nurse or physician to have anything to do with the premature infant that is not absolutely necessary, nor does it justify allowing anyone who has the slightest evidence of respiratory infection to come into the infant's room. Masks are not adequate protection against such obvious carriers of disease. More important than use of masks should be restraint in talking, coughing or sneezing in a nursery for premature infants. The number of bacteria circulating in the air of a room is directly proportional to the number of persons there and the amount of talking, coughing and sneezing that goes on, as well as to the efficiency of masks, which at best is probably poor. One important point we emphasize is that a nurse who has any evidence of a cold should not go on duty in the nursery for premature infants. Unless a sense of responsibility is built up which will make nurses themselves take the initiative in conscientious reporting, these early slight infections may cause much damage. The number of personnel caring for any group of premature infants in 24 hours should be the smallest possible. It is evident that different persons have different bacterial flora, so that the greater the number of persons coming in contact with the premature infant, the greater are its chances of picking up some pathogenic organism.

Nutrition.—The whole problem in feeding premature infants is to give them the food they require without ever overstepping their very limited tolerance to food.

We must often do this without the clinical guides we depend on in larger babies. A little too much food will initiate a nutritional disturbance, diarrhea and perhaps vomiting, and a definite downhill course has started which is difficult to stop, so that if one must make a mistake it is better to underfeed these babies than to overfeed them. The ordinary evidence of appetite is unreliable in many premature infants. The fact that a premature infant refuses its food does not necessarily mean that it cannot digest the food. Premature babies refuse, of course, because they are immature. If we trusted to the evidence of appetite in the smallest infants, we would give them nothing at all, so this reliable guide for feeding as it exists in larger babies is not available to us.

Premature infants are often too weak to suck and swallow effectively. They need not be fed more than every four hours, and they should not be allowed to suck more than 20 minutes for their meal. A nurse can sometimes massage milk from a nipple moved about in a premature infant's mouth so that the bottle becomes empty even though the infant shows little evidence of a sucking reflex. This procedure is wrong because such an infant may aspirate food easily. Premature infants under a certain weight should be fed by gavage as a routine, unless they appear very vigorous indeed. An infant too immature to suck effectively may be too immature to swallow efficiently, and the resulting aspiration of food is a common cause of pneumonia and death in prematurity.

A technic intermediary between the gavage and the ordinary nipple feeding is the use of a Brecht feeder, which should not be forgotten but is safe only when managed by a nurse who understands the deficiencies of a premature infant in swallowing.

Feeding Technic: The technic can be summarized as follows: 1. Gavage feeding is usually indicated for (*a*) all premature infants weighing under 3 pounds, (*b*) premature infants who require longer than 20 minutes to take their calculated feeding, regardless of size, and (*c*) premature infants who are cyanotic or who become cyanotic on being fed. It should be noted that it is often best to give every other feeding by gavage and to administer two thirds of the total formula in the gavage feeding. In strong babies who are starting to show signs of sucking reflex, gavage feeding should be gradually discontinued.

2. The position of the baby while being fed is important. All babies weighing under 4 pounds should be fed in bed with the head elevated on a pillow. Babies weighing over 4 pounds, unless contraindicated, should be picked up and held while being fed.

Caloric Requirements: It has been shown by metabolism studies [65] that premature infants after 10 to 14 days of life require the same total caloric intake as do full term infants. The formula components, i. e., proportions of protein, fat, carbohydrate and minerals, are often modified in respect to the requirements of and the degree of utilization by individual premature infants. Without going into the theory further, it seems wise to feed premature infants on the basis of calories per pound, making 60 calories the upper limit. If formulas are given with the same caloric value of woman's milk, 20 calories per ounce of milk and 3 ounces per pound (about 150 cc. per kilogram) for 24 hours is enough. Although we have related theoretical considerations indicating that woman's milk is not as ideal for premature infants as a cow's milk formula, there is still a place for woman's

milk. If an infant is of such size and vigor and a mother in such condition that it seems probable the infant can be taken home and given breast milk directly in a few weeks, it is certainly important to maintain the mother's breast milk by artificial expression of the milk, even if the milk is discarded. The advantages of direct feeding by breast in the home are great.

The construction of a formula for artificial feeding of the premature is not essentially different from that for a full term and older infant. It is quite possible to feed the premature infant satisfactorily on the same formula of whole milk, with added carbohydrate and water, as would be used for the older child. This formula should give 20 calories per ounce (30 cc.), and one fourth or one third of the total calories should be in added carbohydrates. However, because of the inability of premature infants to utilize fats satisfactorily and their greater need for protein and calcium, it is theoretically advantageous to feed them a formula of partially skimmed milk. Such a formula, made up of milk containing 2 per cent butter fat, which gives about 15 calories per ounce, with added corn syrup, such as karo,® is as follows: 17 ounces (510 cc.) of milk with 2 per cent butter fat and 3 ounces (90 cc.) of a mixture of half karo® and half water. This makes a formula supplying about 20 calories per ounce which is quite satisfactory. However, half-skimmed milk is sometimes difficult to obtain, and it may be more convenient to use one of the similar commercial preparations. Two of them are on the market, one dryco® and the other alacta.® The construction of a formula from dryco® and alacta,® which contain 1.5 per cent fat instead of the 2 per cent fat of half-skimmed milk, is on the same principle. Dryco® has added vitamins A and D. Alacta® does not, although these substances are easily added and additions should be made to formulas constituted of dryco.®

Dryco® or alacta®	9 tablespoons (135 cc.)	20 calories per ounce
50 % karo® solution	2 ounces (60 cc.)	
Water	18 ounces (540 cc.)	

3 ¾ tablespoons (56 cc.) of dryco® = 119 calories per ounce
3 ½ tablespoons (52.5 cc.) of alacta® = 121 calories per ounce

Various standard preparations can be used for the majority of patients, but it is most instructive for the student to write a formula for each infant. However, one stock formula may be used, since most premature infants can be fed the same preparation, with variation in only the amounts and possibly the intervals. The principle involved is to give two thirds or three fourths of the total calories in the concentrated or dried, partially defatted milk and to make up the rest of the calories in carbohydrate, then to add water until a mixture containing 20 calories per ounce is produced. We think that a corn syrup is as good as any other carbohydrate, but a preparation of dextrin and maltose, as dextri-maltose,® is entirely satisfactory and is, in fact, a popular sugar.

Administration of fluids in addition to that supplied by formula should not be necessary for healthy premature infants. The formula should provide 2½ to 3 ounces (70 to 90 cc.) of fluids per pound of body weight. If a premature infant does not take this amount in six feedings, the trouble will be that either (1) the infant is too feeble or immature; in this case it should be fed the proper amount by gavage; or (2) the infant is sick and the diminished intake is an expression of lack of appetite. In this case the infant should be handled as any sick infant, its caloric intake should be reduced and extra fluid given between feedings, or very likely it should be given fluids parenterally.

Feeding Schedule: The frequency of feeding and amounts fed to newborn babies are as follows: Nothing is given by mouth in the first 24 hours after birth. Then feedings are begun with ½ ounce (15 cc.) of 5 per cent dextrose in water every four hours for two or three feedings. Mother's milk or a diluted skim milk formula supplying 10 calories per ounce is then substituted. This is gradually increased as shown in table 23 and can be modified for the very small or the large, vigorous baby as the case may be.

When the infant's weight reaches 4½ pounds (2,041 Gm.) and it is taking the feedings well by nipple (60 calories per pound per 24 hours), an evaporated milk formula containing added water and 50 per cent corn syrup solution is substituted, which supplies at first 45 to 50 calories per pound. If this is well tolerated, the caloric intake should be increased to 60 calories per pound per 24 hours within three days, if the physician thinks this amount is necessary for good gain.

Vitamin Additions: On theoretical but not clinical evidence 100 mg. daily of ascorbic acid should probably be given in the formula, beginning on the second day, until the baby is 2 months old; thereafter, 50 mg. daily is ample.

TABLE 23.—*Representative Feeding Schedule for Premature Infants* *

Newborn Infants		Infants Over 1 Wk. Old on Admission		
Day of Life	Calories per Pound per 24 Hr.	Fluid Intake per 24 Hr. in Ounces per Pound	Day of Admission	Calories per Pound per 24 Hr.
1st	0	...	1st	0 to 30
2d	10	1 to 2	2d	20 to 40
3d	20	2	3d	40 to 60†
4th	30	2½	...	.....
5th	40	2½	...	.....
6th to 10th	50	2½	...	.....
After 10th	55 to 65	3	...	.....

* From the Pediatric Department, University Hospital, Ann Arbor, Mich.
† The upper limit of 60 calories per pound of body weight per day should rarely be exceeded.

Vitamins A and D should be given after 2 weeks of age to supply 6,000 to 8,000 units of vitamin A and 2,000 to 3,000 units of vitamin D. Some feeble infants at 2 weeks of age cannot safely be given 20 drops of oil. Water-miscible vitamin preparations (A and D) are now available.

Iron: Most premature infants show a considerable drop in the hemoglobin content of the blood from a high level (15 to 22 Gm.) at birth to a low level of actual anemia (7 to 10 Gm.) at about 10 weeks. The theoretical considerations which guide therapy are presented in the section on "Hemopoietic System and Iron Metabolism."

Inorganic iron in the form of a ferrous salt preparation should be supplied beginning at 2 weeks to 1 month of age. The usual dose is approximately 3 grains (0.19 Gm.) daily, most easily administered in the form of the elixir.

Control of Environment.—Premature infants need a relatively high environmental temperature and a relatively high humidity, but it is less commonly realized that a premature infant's body temperature will rise above normal with as little provocation as it will fall below normal. There is a great tendency to keep babies too warm. A constant body temperature, even though it is subnormal (96 to 97 F.), is usually safer than a higher but irregular temperature.

To have a properly and automatically regulated environment is of great aid. A high humidity can partially compensate for a low environmental temperature, but the converse of this is not true: for example, 25 per cent relative humidity and a temperature of 95 F. are harmful. An incubator temperature of 80 to 85 F. and humidity of 50 to 60 per cent are most desirable.

One of the simplest incubator devices is, of course, a bassinet so draped that it makes a tent to be heated by electric lights. Armstrong incubators are satisfactory and relatively inexpensive. The Chapple type of bacteria-tight incubator is theoretically of great value but is very expensive.

Indications for Use of Incubator: Use of the incubator is indicated for (1) small premature infants weighing under 3 pounds who need more heat and humidity than other infants and (2) premature infants with infection. (Babies over 48 hours old on admission should be considered as exposed to infection.)

Method of Correct Use of Incubator: 1. One should stabilize the temperature of the incubator at 80 to 85 F. with a relative humidity of 55 to 65 per cent before placing the baby in it. Levels above this are seldom needed, and changes should not be made frequently. 2. Increasing or decreasing the heat in an incubator should be carried out only after due consideration has been given to the average of the infant's temperature for the preceding 24 hours and not after a single temperature reading. Exception to this rule can be made when the body temperature is low (below 95 F.). Treatment of excessively low temperatures (below 95 F.) should be carried out under the direction of the attending physician. In cases of low temperature, radiant heat carefully given until the baby's temperature reaches 97 F. is useful.

Oxygen Administration: On theoretical grounds it seems probable that any small premature infant may benefit from an increase in oxygen in the inspired air. The administration of oxygen to all premature infants under 3½ pounds (1,600 Gm.) is a practical empirical rule. Any premature infant suffering from dyspnea and/or showing such gross signs of anoxia as cyanosis should obviously receive additional oxygen.

A concentration of 40 to 50 per cent oxygen usually suffices when additional oxygen is indicated. This concentration can usually be attained in a good incubator with a flow of 4 to 5 liters per minute from the oxygen supply tank. It is advisable to check the oxygen concentration in the incubator with an oxygen analyzer. Adequate oxygen can also be supplied through a hood or large cone made with old roentgen film or plastic sheets.

General Considerations: The following general statements can be made concerning control of the premature infant's environment: 1. High body temperature and sharp fluctuations in temperature are detrimental.

2. Stabilization of body temperature is more important than the maintenance of any definite level. During the first two or three weeks of life, fluctuations of body temperature between 96 and 99 F. are apparently quite normal for babies of these weight groups. Levels below this should cause no alarm unless evidences of unsatisfactory progress are present.

3. As the infant gains in age and weight, the average body temperature may be expected to rise gradually. (Sick premature infants are prone to show extremely low or extremely high temperatures.)

4. A rapid rise of temperature, even from low levels, should not be permitted. A rise of a degree an hour from levels of 93 or 94 F. is maximum, and less rapid rise is better.

Diagnosis and Treatment of Illness.—General Considerations: The reaction of premature babies to any infection is apt to be nonspecific. It should be remembered that the temperature course cannot be trusted. A newly appearing irregularity in temperature or a drop in temperature not due to a change in environmental temperature or humidity is more likely to indicate an infection than a definite elevation. Listlessness, diminished activity, more feeble sucking reflex, alteration in appearance, regurgitation or vomiting must always be suspected as early signs of infection. The response to infection is apt to be the same wherever the focus, and one should not demand evidence of dyspnea in pneumonia, abdominal pain in peritonitis or earache in otitis media. As with larger babies, lessened interest in food is an important symptom, but its significance depends on the previous state of responsiveness. To a good nurse who has evaluated such feeble evidence of appetite as the sucking of a premature infant on a gavage tube, the smallest variation in this activity may be of significance. Increased number and change in character of the stools are the most consistent signs of infection in premature infants and lead to a rapid loss of fluid.

Hyperpnea may appear as an evidence of acidosis, but, since premature babies breathe irregularly anyway and often have short periods of hyperpnea with alternating apnea, one has to be particularly careful in evaluating such signs. Failure to gain, or loss in weight, usually follows the onset of these symptoms. In spite of the difficulty in making specific diagnoses, it is generally quite easy for a physician familiar with these infants to recognize illness and signs indicating that infection is the cause of the illness.

Roentgenograms, blood cultures, blood counts, stool cultures and other diagnostic procedures may be indicated as with older babies, but their interpretation must always be made in the light of the premature state.

At the first appearance of the signs of an incipient nutritional "break," the food intake should be either partially reduced or omitted, depending on the estimated severity of the disturbance. In most cases, it would be sufficient to reduce the caloric value to about one half and fluids (dextrose or saline and dextrose solutions) should be offered at the two hour interval between feedings. If the break is severe and associated with diarrhea, it may be necessary to omit all feedings containing milk and to give only water or dextrose and saline solutions, with gradual resumption of adequate caloric intake. With severer diarrhea even this is too much, as anything taken by mouth stimulates peristalsis, and one must resort to parenteral administration of fluids. The management of the sick premature infant follows the general principles for care of babies of all sizes with nutritional breaks, except that with premature babies one is handicapped by the baby's size and its lack of reserve in body proteins and in fat.

Parenteral Administration of Fluids: In sick babies the administration of fluids parenterally may be used to supplement fluids given by mouth or as a complete substitute. In general, about 3 ounces per pound is a maximum in 24 hours, but somewhat more may be necessary to repair an initial loss of fluid. Continuous intravenous injections, although ideal, are usually impractical in small premature infants, as it is impossible to run them slowly enough to prevent over-

loading the circulation. Sets of fluids (injection of 15 to 20 cc. of saline solution per pound interstitially and of 10 cc. of dextrose solution per pound intravenously immediately afterward) must be relied on. For theoretical reasons, in cases of hyperpnea in which it seems wise to give extra base, it is better to rely on sodium bicarbonate and saline solution administered intravenously than on lactate solutions.

Transfusion: Transfusions play an important part in the treatment of the sick premature infant. Although in many instances it may be wise to give only the plasma rather than the whole blood, the decision should be reached on the basis of the estimated need for red blood corpuscles. When red blood cells are not required, the indications for giving plasma alone are (1) to repair a serum protein deficit, which is almost always present in premature infants and is quickly aggravated by the parenteral administration of fluids, and (2) to give adult antibodies which reasonable conjecture makes one believe would be beneficial. When for supposed antibody content, plasma from fresh, matched blood should be given rather than pooled, stored plasma. Transfusions are usually indicated in sick premature babies. It is better in dehydrated babies first to administer the ordinary fluids parenterally before giving the transfusion. Whole blood transfusions are usually indicated in older infants, since we expect their hemoglobin concentration to be low.

Cross matching and typing of the blood should be done before transfusion of the premature infant as for any other baby. Although it is possible to give transfusions to very young premature infants successfully without matching the blood, it is wisest to avoid all risk, so that if any reaction does occur one can be sure it is not due to negligence.

Chemotherapy: Chemotherapy has been felt to be of definite value in the treatment of infections in premature infants. The prophylactic administration of sulfonamides at the first appearance of a "danger sign" is justifiable because of the rapidity with which infections develop and spread in these babies. The placing of a dose of the sodium salt of sulfadiazine in the formula has been found to be the most convenient method of administration, and adequate blood levels (5 to 10 mg. per 100 cc.) are easily obtained. Sulfadiazine sodium should be given cautiously according to weight. From data showing that premature infants have a decreased sulfonamide clearance, with relatively high blood levels on smaller dosages, ½ grain (0.03 Gm.) per pound per day is usually adequate. Parenteral administration should be used if necessary, but with extreme caution. Insure a fluid intake at least 2 ounces per pound when sulfonamides are given.

A combination of penicillin and sulfadiazine, or of sulfadiazine and streptomycin in certain indicated cases, may be of benefit. The development of new and better drugs to combat infection is constantly widening the potentialities of approach to effective therapy of the premature infant. Aureomycin now appears to be a most promising and effective antibiotic agent for use in many cases.

Recognition of Syphilis: The problem of the recognition of syphilis in the premature baby needs special mention. Although the general principles of diagnosis apply to any baby, the difficulty is somewhat greater in the premature infant. As with other newborn babies the serologic test reaction may be negative for some time after birth, although the baby has syphilis. Even though as high a percentage of premature infants in this country do not have syphilis as used to be believed, and it is one of the rarer causes of prematurity, prematurity may be a result of

syphils. Therefore, one must always routinely exclude this diagnosis for any premature baby.

Probably 80 per cent of babies with syphilis have some changes in their long bones that can be recognized as abnormal, although not so many demonstrate changes that are specific or pathognomonic for syphilis. Roentgenograms of the long bones are taken routinely to diagnose syphilis before the serologic reaction is dependable. Likewise, study of the spinal fluid of newborn infants shows abnormal changes in about one third of the cases of syphilis, and this often may lead to a diagnosis before the serologic test gives a specific reaction.

On the other hand, a positive serologic reaction may be passively transmitted from the mother and may not be an indication of active spirochetal processes in the baby. A careful evaluation of the quantitation of the serologic test is necessary before a baby with no other symptoms can be assumed to have syphilis. Although the reactions to the serologic tests are still of great value, they are less reliable at this age, and other evidences of an active syphilitic process must be depended on for diagnosis.

News and Comment

ANNOUNCEMENTS

First Comunication of the General Secretary, International Pediatric Association.—The third pamphlet of the Sixth International Congress of Pediatrics, with the abstracts of lectures and all of the communications and discussions, is finished. This volume will be sent to the different national pediatric associations for distribution free of charge among the conference members with cards series A and C, who are requested to apply to their pediatric association in this matter.

All those interested in this literature, such as physicians, libraries and clinics, may obtain either the three single volumes for 25 Swiss francs or the three volumes bound together for 27 Swiss francs. The congress transactions will be edited by the General Secretary's Office, International Pediatric Association and sent to the applicants after payment has been received. If more than 10 copies of the whole transactions are ordered, a reduction of 20 per cent will be granted, and if more than 20 copies, a reduction of 30 per cent. Orders may be forwarded to the General Secretary's Office, Kinderspital, Zurich 32. Payments should be made to the account of the association with the Zürcher Kantonalbank, Zurich.

A certain number of the transactions of the Fifth International Congress of Pediatrics, New York, 1947, may still be obtained from Messrs. Almquist and Wiksell, Editors, Uppsala, Sweden, for the reduced price of 10 Swedish crowns.

G. Fanconi
General Secretary, International
Pediatric Association

GENERAL NEWS

A virus research laboratory that will concentrate on childhood infections has been established at the University of Louisville School of Medicine. Its completion was effected by a grant from the recently organized Kentucky Child Health Foundation. The investigations will be supervised by Drs. Alex J. Steigman and James G. Shaffer of the school's Child Health and Bacteriology Departments.

SPECIAL NOTICE

For the general information of indexers, catalogers and library personnel with reference to the listing of the new title of this journal, we advise that the *Quarterly Cumulative Index Medicus* policy be followed. The *Quarterly Cumulative Index Medicus* with its volume 49 (January-June 1951) will list this journal under the new title, so that the letters A. M. A. will be included as an integral part of the title. For the completion of volume 48 (July-December 1950) the *Quarterly Cumulative Index Medicus* will continue to use the old title, without adding the designation A. M. A.

CORRECTION

In the article on "Electrocardiograms of Normal Children" by Drs. John L. Switzer and Manuel Besoain, in the March issue, page 449, Dr. Besoain was incorrectly referred to as a Postdoctorate Research Fellow of the National Heart Institute. In actuality he was a Fellow from the Division of International Health of the U. S. Public Health Service.

Abstracts from Current Literature

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

Relationship Between Rh Factor and Meconium Ileus. E. Ziegler, Helvet. pædiat. acta **2**:296 (June) 1947.

A case of meconium ileus is described in which an attempt to remove the meconium mechanically resulted in a tear of the serosa during the operation and consequent peritonitis. At the autopsy chronic interstitial pancreatitis and bronchiectasis were observed. Rh incompatibility could be excluded with certainty in this case.

From the Author's Summary.

Biliary Peritonitis Without Perforation of the Gallbladder in Typhoid. Laura Landucci, Pediatria **57**:73 (Jan.) 1949.

In the third week of typhoid, a 3 year old child had peritonitis associated with jaundice and pain in the upper right quadrant. Although the peritonitis was clearly due to bile, no perforation of the gallbladder was seen at operation; however, a necrotic patch 5 cm. long was observed on its surface. The gallbladder was aspirated and then opened and the opening sutured to the abdominal wall. At first there was copious discharge of bile from the fistula; healing occurred in one month, however. Only 4 other cases are described in the pediatric literature.

Higgins, Boston.

Acute Intestinal Occlusion from Ascarides. Sulas Vincenzo, Policlinico inf. **16**:190 (April) 1948.

The author discusses acute intestinal obstruction caused by worms on the basis of a personal case (of a child 3 years old with successful operation) and of the few other cases described up to the present in the literature. He points out that in these cases the diagnosis is difficult and surgical intervention is often necessary before diagnosis can be made.

From the Author's Summary.

The Appendix and Appendicitis in the Newborn and the Nursling. Pietro Majone, Policlinico inf. **16**:293 (July) 1948.

The author studied 81 appendixes of newborn infants and nurslings, macroscopically and microscopically, selecting the most important points and presenting some data and personal observations. He examined 2 appendixes in serial sections, the first one in about 900 sections and the second in 700 sections, observing the structure of the layers and their components in various parts of the organ from end to end. He noted the relation between the size of appendix and that of thymus and spleen in the same persons. From the results of these studies, he showed that the structure of the appendix plays an interesting role in the rarity of appendicitis in the first months of life.

From the Author's Summary.

Hepatic Dwarfism. Policlinico inf. (supp.) **15**:1 (Jan.) 1947.

The authors present a revision of the symptomatologic picture of glycogenosis (von Gierke's disease) and a critical analysis of the clinical and humoral connections between this disease and the other chronic hepatic diseases of children

in the general picture of hepatic dwarfism. They base their study on a case of glycogenosis with enlargement of the heart and liver which presented an atypical clinical and biochemical symptomatology: poor nutritional state, no noticeable collection of subcutaneous fat on the face and trunk, hepatoparenchymal jaundice, hemorrhages, enlargement of the spleen, urobilinuria, bilirubinuria, choluria, glycosuria, absence of acetonuria, prolonged bleeding and clotting times, hyperbilirubinemia and a positive delayed reaction to the direct van den Bergh test. A biopsy specimen of the liver showed conspicuous glycogenosis and an increase of connective tissue.

The authors analyze each proved case of glycogenosis by recording not only the classic symptoms but also the atypical findings. They come to the conclusion that, contrary to the general opinion, even the most important symptoms often are of no value and that one encounters with the same frequency clinical and humoral findings that do not belong to the picture of this disease but to the symptomatology of other hepatic diseases, leading, according to the classic schemes, to hepatic functional alterations much severer than those present in glycogenosis.

The authors then analyze the clinical symptoms described as characteristic of glycogenosis. They conclude that dwarfism presenting particular constitutional findings—good nutritional state with a near normal collection of subcutaneous fat on the trunk and face, flabby and hypotrophic musculature, cutaneous alterations, hypotrophy of the genitalia, delayed and deficient puberal development, delay in walking, peculiar mode of walking, retardation in ossification of carpal centers, osteoporosis, rickets, anemia with lymphocytosis and diuresis—is to be observed not only in glycogenosis but, frequently, in every chronic hepatic disease of childhood which damages a great part of the liver cells. Such symptoms, therefore, belong to the picture of hepatic dwarfism whatever may be the anatomicopathologic substrate of the hepatic damage.

The authors point out that in children cirrhosis of the liver, which is the most frequent cause of hepatic dwarfism, is often asymptomatic for years, owing to the remarkable regenerative power of children's hepatic tissue. Cirrhosis often manifests itself quite suddenly in its full symptomatology (jaundice, ascites) only in the terminal stage of the disease. They then report several cases of hepatomegalic cirrhosis from the world literature, in which a clinical and biochemical picture was encountered that, even in the symptoms of disturbance in carbohydrate metabolism, was nearer to the classic picture of glycogenosis than the majority of proved cases of the disease.

The authors discuss hepatic steatosis and point out that, besides the well known secondary forms, other "idiopathic" congenital forms with a subacute course have been described. These forms not only have the clinical picture of hepatic dwarfism without the common symptoms of steatosis (fever, anorexia, jaundice, urobilinuria) but also present alterations of the carbohydrate metabolism similar to those described as characteristic of glycogenosis. These forms of hepatic dwarfism differ clinically from glycogenosis in their rapid course and profound effect on the nutritional state and general health. But it is exactly the presence of a good nutritional state and of perfect general health that characterizes a third type of hepatic steatosis. This type, with the exception of these symptoms, has the same picture as the subacute form; that is, therefore, a form of hepatic steatosis which does not at all differ from hepatic glycogenosis.

The authors explain the reason that in cirrhosis and steatosis of the liver those symptoms of a disturbance in carbohydrate metabolism described as characteristic of glycogenosis are so frequently met. Up to the present, the clear relation

between the biochemical picture (particular disturbances of carbohydrate metabolism) and the anatomicopathologic findings (storage of glycogen in the liver; inability of the liver to utilize its glycogen) in glycogenosis has led to the conclusion that these symptoms are pathognomonic or quasipathognomonic of glycogenosis and to the diagnosis of this disease in each case of hepatomegalic dwarfism presenting the aforementioned biochemical peculiarities. After a discussion of each of these symptoms (hypoglycemia, hyperacetonemia and acetonuria; particular alterations of the blood sugar tolerance curves; subnormal response of blood sugar to epinephrine; increased sensitivity to insulin) in the general picture of hepatic diseases, the authors conclude that these symptoms are frequent in glycogenosis because of its particular histopathologic substrate, though they may be present in any hepatic disease that causes diffuse parenchymal damage and, therefore, seriously disturbs the carbohydrate metabolism. In hepatic dwarfism, owing to the severe chronic lesions which are the basis of the whole clinical picture, all these symptoms appear so frequently as to play the most important role among the biochemical manifestations of the syndrome, even in the absence of hepatic glycogenosis.

The authors dsecribe the various functional tests used for a differential diagnosis among the forms of hepatic dwarfism, and particularly between glycogenosis and cirrhosis, and conclude that none of them is reliable, since they are based on a presupposed functional integrity of the glycogenotic liver in opposition to a functional insufficiency of the liver in other hepatic diseases. In reality in glycogenosis not only the carbohydrate metabolism, as was previously affirmed, but also the fat and protein metabolism, the blood coagulation, the disintoxicating function and the water metabolism are disturbed, so that by degrees the clinical picture resembles cirrhosis rather than glycogenosis.

Up to now nearly all cases of hepatomegalic dwarfism were described as glycogenosis, though in the absence of a histologic examination. The authors accept all these cases as merely of hepatomegalic dwarfism. They point out that in each of them, instead of the symptoms described as characteristic of glycogenosis, only the numerous atypical features appear, contrary to the classic description of the disease. They analyze the hepatic dwarfism due to steatosis or to glycogenosis which is described sometimes in patients with diabetes mellitus. They also report a case observed by them of a boy 7 years of age.

The authors finally discuss the hepatomegalic dwarfism described by Ylppö as due to a "diffuse alteration of adenomatous type of the liver cells," the hepatomegalic dwarfism described by Boudet, Boucomont, Balmes and Cazal as due to phospholipid storage in the parenchymal cells of the liver and the hepatomegalic dwarfism due to chronic "idiopathic" and amyloidosis of the liver.

FROM THE AUTHORS' SUMMARY.

GASTRIC ULCER IN YOUNG SUBJECTS. PIETRO AMISANO, Policlinico inf. (supp.) **16**:1 (Jan.) 1948.

The author explains the greater frequency of gastric ulcer in young subjects that has been noted in the last ten years as due to a more exact interpretation of the clinical symptoms and a more rational employment of roentgenologic examination. In the case described by him the manifest symptoms began in the patient at the age of 10 years. She was 16 years old when first seen, poorly developed, with absence of menstruations and of the apparent age of 12 years. Surgical intervention confirmed the diagnosis of a prepyloric ulcer with a serious pyloric stenosis. The postoperative progress was particularly interesting. She had a

rapid increase in body weight and within a few months the menstrual flow appeared. Within two years afterward, the patient reached normal bodily and psychologic development.

Besides the important pathogenetic factors which the author presents, there should be stressed the poor development of the patient which was due to the gastric ulcer and its effects on nutrition. In effect the gastroenterostomy restored the gastric function to normal and aided the bodily and psychologic development.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF ATROPHIC INFANTS WITH DESOXYCORTICOSTERONE ACETATE. FORSELL, Ann. med. int. Fenniae **36**:247, 1947.

Four infants, 1 to 12 months of age, were underweight because of acute infections or dyspeptic stools. The administration of desoxycorticosterone acetate (percorten®), in a maximum total dose of 5 mg., brought about an increase in body weight. The drug is considered to reestablish the fluid-binding functions and to increase the tolerance to food.

WALLGREN, Stockholm, Sweden.

THREE CASES OF CONGENITAL MEGACOLON. H. MOLTRUP POULSEN, Nord. med. (Hospitalstid.) **33**:299 (Jan. 31) 1947.

Three children, aged 15, 8 and 15 years, respectively, with congenital megacolon were treated by resection of the sympathetic trunk with satisfactory results in the first child. The second patient had previously been treated with resection of colon, and in the third child, who showed only slight improvement, the operation probably led only to incomplete interruption of the sympathetic supply to the affected part of the intestine.

WALLGREN, Stockholm, Sweden.

RESULTS OF SURGICAL TREATMENT OF CONGENITAL MEGACOLON. JOHAN WALDE, Nord. med. (Med. rev.) **33**:374 (Feb. 7) 1947.

This is a report on 5 patients, of whom 4 were treated by sympathectomy. The fifth patient died before any surgical procedure could be performed. Two of the patients operated on improved; the condition of the other 2 remained unchanged. In 1 of the latter relaparotomy with resection of the colon and end to side anastomosis was done. In a table of data on 421 patients treated according to different methods, it ensues that sympathectomy gives the best results and the lowest mortality (3 per cent). The results of sympathectomy are frequently not so satisfactory on account of technical difficulties. Other surgical methods, resection and anastomosis, give poorer results and the mortality is high (30 per cent). The author cites the results of Anschütz (*Zentralbl. f. Chir.* **58**:192 [April 11] 1931) with resection and anastomosis two to six months after creation of an artificial anus (of 16 patients 15 were free from symptoms and only 1 died).

WALLGREN, Stockholm, Sweden.

THREE CASES OF FIBROCYSTIC DISEASE OF PANCREAS. ALF ÖDEGAARD, Nord. med. (Norsk mag. f. lægevidensk.) **33**:440 (Feb. 14) 1947.

Three typical cases of fibrocystic disease of the pancreas are reported. The diagnosis was made post mortem.

WALLGREN, Stockholm, Sweden.

SURGICAL TREATMENT OF MEGACOLON. IVAR R. SANDBERG, Nord. med. (Hygiea) **33**:445 (Feb. 14) 1947.

Three patients with congenital megacolon are reported on who were treated with sympathectomy with a temporary satisfactory result. One of the children was free from symptoms for four years, then there was a gradual relapse to the status before operation. In 2 of the patients a secondary resection of the whole or of the greater part of the affected colon had to be performed. The author warns against exaggerated optimism regarding neurosurgical treatment of megacolon.

WALLGREN, Stockholm, Sweden.

GASTRIC AND DUODENAL ULCERS IN CHILDREN OF SCHOOL AGE. FORSELL, Nord. med. (Finska läk.-sällsk. handl.) **34**:1162 (May 16) 1947.

Gastric ulcer in a boy 12 years of age and duodenal ulcers in 6 children (4 boys and 2 girls) 9 to 14 years of age are reported.

WALLGREN, Stockholm, Sweden.

INTESTINAL ATRESIA. B. C. BRYNJULFSEN, Nord. med. (Med. rev.) **36**:2401 (Nov. 28) 1947.

Several patients with atresia of the intestine are reported on. In 2 the condition was localized to the duodenum (fatal outcome) and in 2 to the small intestine. Of the latter, 1 died and the other was successfully operated on on the eighth day of life. He was discharged from the hospital in a healthy state ten days later (probably the ninth patient cured of a disorder of this kind).

WALLGREN, Stockholm, Sweden.

ACUTE MALIGNANT GASTROENTERITIS. OLUF ANDERSEN, Nord. med. (Hospitalstid.) **36**:2433 (Dec. 5) 1947.

Since 1943 there have been reported 650 cases of epidemic diarrhea in infants in Denmark, with a fatal outcome in 250 cases. The disease is considered to be a virus infection with symptomatic diarrhea. There is no sign of an inflammatory process in the intestine. The disease is principally air borne, but enterogenous infection through contaminated stools and healthy virus carriers cannot be excluded. The incubation period is five to ten days, sometimes more. The symptoms are diarrhea with fluid or only slightly looser stools than normal, containing no blood or pus, and only exceptionally mucus. Vomiting is noted only occasionally. The temperature is often elevated. Great deterioration in the general condition is present, sometimes already at the onset. The infants examined were toxic and dehydrated and had a gray pallor. Severe acidosis was frequent. Cerebral signs were observed in 10 per cent of the infants. The course of the disease was sometimes extremely rapid, sometimes slower. Most deaths occurred during the first week. Relapses occurred in some patients one to two weeks after the manifestation of the disease. The acute symptoms disappeared generally in one week; the hospital treatment lasted from three to eight weeks. Postmortem examination was performed in 43 children. In no child were there any intestinal lesions. Eleven infants were examined in regard to cerebral changes and all of them displayed edema, meningoencephalitis, perivascular infiltrations or hemorrhage in the meninges or parenchyma. Probably the cerebral involvement is a central factor in this disease.

WALLGREN, Stockholm, Sweden.

TREATMENT OF DYSPEPSIA WITH CAROB FLOUR. ROBERT LANDOLT, Svenska läktidning. **44**:916 (April 18) 1947.

Twenty-seven patients with acute dyspepsia (22 infants and 5 small children) were treated with a 10 per cent solution of "arobon" (powdered fruit of the locust tree, Ceratonia siliqua) in the following way: After eight to twelve hours' fasting, 100 cc. of "arobon" solution per kilogram of body weight and an additional supply of fluid were given perorally. The "arobon" solution was then gradually supplemented by skimmed acid milk and by whole citric acid milk. By one and a half days after the treatment was started the stools were normal; there were no relapses. The author maintains that the treatment of acute dyspepsia with "arobon" is valuable and simple.

WALLGREN, Stockholm, Sweden.

ACIDOSIS IN ACUTE GASTROENTERITIS IN INFANTS. AXEL V. MÖLLER and V. POSBORG PETERSEN, Ugesk. f. læger. **109**:837 (Nov. 20) 1947.

Bicarbonate determinations of the blood according to the method of van Slyke and Neill on 32 infants with acute dyspepsia are reported. Seventeen displayed a severe acidosis of 10 millimoles, 10 a less severe acidosis of 10 to 16 millimoles and 3 a slight acidosis of 16 to 20 millimoles. There was no relation between the duration or severity of the illness and the degree of acidosis.

WALLGREN, Stockholm, Sweden.

Psychology and Psychiatry

THE CHOREIFORM SYNDROME: ITS SIGNIFICANCE IN CHILDREN'S BEHAVIOR PROBLEMS. ARTHUR R. TIMME, California Med. **68**:154 (March) 1948.

In this presentation the author has tried to point out certain organic factors that enter into the formation of a majority of school behavior problems. These factors are not readily apparent but can be discovered by careful neuroendocrine examination correlated with an understanding of the behavior sequence. They are factors that are operative in spite of normal intelligence, good general health and, even, favorable home environment. They are in the main disturbances of concentration and attention, with a deficiency of emotional control, particularly the rage reaction. Hostile and aggressive behavior is facilitated by these defects, even though its form and content are determined by unconscious factors based on parent-child relationships. Not being well understood, these children are subjected to the same pressure and requirements as their normal siblings and mates. The resultant rebellious or withdrawn behavior is misinterpreted or futilely treated; trouble begins to pile up, and delinquency is in the offing. When they are properly understood, however, the impossible is no longer expected of them. Often, medical treatment of the apparent neurophysiologic disturbances, along with proper adjustments of psychologic relationships in the environmental patterns, brings about an increasing improvement, aided and abetted by normal physiologic growth. Then the beginning of a favorable readjustment is at hand.

PRYOR, Redwood City, Calif.

COMMON BEHAVIOR DISTURBANCES IN THE FIRST TWO YEARS OF LIFE. BENJAMIN SPOCK, J. A. M. A. **136**:811 (March 20) 1948.

The advantages of the "rooming-in" arrangement are discussed, as well as the "self-regulated schedule" and the hazards of early weaning. After the automatic cooperation of their child during the first year, parents are usually unprepared to

cope with the increased activity, the self-asserting independence and the clinging dependence becoming manifest in the second year of life. Suggestions to ease these difficulties are made.

KIMBALL, Evanston, Ill.

Diseases of the Ductless Glands: Endocrinology

EFFECT OF THYROIDECTOMY ON THE CONVERSION OF CAROTENE TO VITAMIN A. VICTOR A. DRILL and ALDO P. TRUANT, Endocrinology **40**:259 (April) 1947.

Indirect evidence in the literature indicates that the conversion of carotene to vitamin A may be impaired during experimental hypothyroidism. It remained, however, to test this hypothesis by using purified diets and by observing whether thyroidectomized animals receiving carotene but no vitamin A would show signs of vitamin A deficiency. In the experiments reported herewith it was observed that thyroidectomized rats receiving only carotene as a source of vitamin A had signs of vitamin A deficiency.

It is apparent that the thyroid gland plays a major role in the conversion of carotene to vitamin A.

JACOBSEN, Buffalo.

REGULATION OF PITUITARY ADRENOCORTICOTROPHIC ACTIVITY DURING THE RESPONSE OF THE RAT TO ACUTE STRESS. GEORGE SAYERS and MARION A. SAYERS, Endocrinology **40**:265 (April) 1947.

The excitatory effect of nonspecific stress on the secretory activity of the adrenal cortex is mediated through the anterior lobe of the pituitary. The effect is manifested promptly, there being an appreciable reduction in the ascorbic acid concentration of the adrenal gland within an hour after the beginning of exposure of the organism to noxious stimuli. The present paper is concerned with the mode of action of acute stress in modifying the rate of elaboration of adrenocorticotropic hormone by the anterior part of the pituitary as measured by the alterations in the ascorbic acid content of the adrenal.

It was found that the increase in the rate of elaboration of adrenocorticotropic hormone by the pituitary during exposure of the rat to stress for one hour or less is proportional to the decrease in the concentration of adrenal ascorbic acid which accompanies such exposure.

Adrenal cortex hormone, administered immediately before exposure of the rat to any one of a number of stresses (cold, heat and injection of histamine, epinephrine or killed typhoid organisms), suppresses the enhanced adrenocortical activity which otherwise follows such an exposure.

The results have been interpreted to mean that the anterior lobe of the pituitary elaborates adrenocorticotropic hormone at a rate inversely proportional to the concentration of cortical hormone(s) in the body fluids and according to the requirements of the peripheral tissue cells for cortical steroids.

The data suggest, but do not offer conclusive proof, that the cortical steroids act directly on the anterior part of the pituitary rather than indirectly through products of their metabolic activity or their deficiency.

JACOBSEN, Buffalo.

THE ROLE OF THE ADRENAL CORTEX IN MAMMARY DEVELOPMENT AND ITS RELATION TO THE MAMMOGENIC ACTION OF THE ANTERIOR PITUITARY. A. T. COWIE and S. J. FOLLEY, Endocrinology **40**:274 (April) 1947.

The possible involvement of the adrenal cortex in mammary development was first indicated by experiments which showed that desoxycorticosterone promoted growth of the mammary ducts in immature male mice. The clear indication that

one at least of the specific adrenal cortex steroids will evoke mammary growth, taken in conjunction with the fact that the cortex is stated to be capable of secreting androgen and estrogen, the mammogenic properties of which are well known, made it advisable to investigate further the effects of adrenalectomy on the mammary gland.

The results of the experiments on rats here reported in general add to existing evidence that extracts of the anterior lobe of the pituitary contain factors which can cause development of both mammary ducts and alveoli by direct action on the mammary gland, and it appears that they can do this without the aid of steroid sex hormones arising from either the gonads or the adrenal cortex.

JACOBSEN, Buffalo.

EFFECTS OF TESTOSTERONE PROPIONATE ON BODY WEIGHT AND URINARY NITROGEN EXCRETION OF NORMAL AND HYPOPHYSECTOMIZED RATS. GILBERT S. GORDAN, HERBERT M. EVANS and MIRIAM E. SIMPSON, Endocrinology **40**:375 (June) 1947.

The effects of testosterone propionate U. S. P. on body weight and urinary nitrogen excretion of normal and hypophysectomized adult female rats were studied.

With 0.5 mg. of testosterone propionate per day, but little reduction of nitrogen excretion occurred in both normal and hypophysectomized rats. The hypophysectomized rats failed to gain weight on this dose, while the intact rats gained 10 Gm. in five days.

With 2.5 mg. of testosterone propionate, both normal and hypophysectomized rats retained a significant and equal amount of nitrogen. With this dose, the intact animals continued to gain weight notably, while the hypophysectomized rats gained but 4 Gm. in five days.

It appears that testosterone propionate produces an equal amount of nitrogen retention in normal and hypophysectomized rats, but that utilization of the retained nitrogen to form body weight differs greatly in these two groups, being much greater in the intact animals.

JACOBSEN, Buffalo.

THE EFFECTS OF HYPOPHYSECTOMY ON GASTRIC ACIDITY OF ADULT FEMALE RATS. ROGER C. CRAFTS and BURNHAM S. WALKER, Endocrinology **40**:396 (June) 1947.

Hypophysectomy induces anemia in adult male or female rats. This anemia is microcytic and hypochromic, accompanied with hypoplasia of the bone marrow. Injections of a combination of thyroxin, iron and copper alleviated the anemia. This suggests that the metabolism of iron may be disturbed following hypophysectomy. Normal gastric acidity is generally recognized as a significant factor in iron absorption. This paper is concerned with changes in the acidity of gastric secretion following removal of the hypophysis.

It was observed that hypophysectomy induced a decrease in the volume of gastric secretion which was not caused by the anemia that followed hypophysectomy.

JACOBSEN, Buffalo.

THE IODIDE CONCENTRATING MECHANISM OF THE RAT THYROID AND ITS INHIBITION BY THIOCYANATE. J. E. VANDERLAAN and W. P. VANDERLAAN, Endocrinology **40**:403 (June) 1947.

The observation is confirmed that the thyroid gland depleted of hormonal iodine under the influence of propylthiouracil is still capable of concentrating large quantities of iodine when potassium iodide is injected.

JACOBSEN, Buffalo.

CYTOCHEMICAL EVIDENCE FOR THE CESSATION OF HORMONE PRODUCTION IN THE ZONA GLOMERULOSA OF THE RAT'S ADRENAL CORTEX AFTER PROLONGED TREATMENT WITH DESOXYCORTICOSTERONE ACETATE. ROY O. GREEP and HELEN WENDLER DEANE, Endocrinology **40**:417 (June) 1947.

Combined morphologic and cytochemical studies have revealed that the zona fasciculata of the adrenal cortex may atrophy, become hyperactive or become exhausted without any conspicuous alteration in the zona glomerulosa. The interpretation placed on these findings is that the adrenal cortex is composed of two separate secreting zones which produce different types of cortical hormones. The distinction between the two zones is shown again in the observations reported in this paper.

Injections of 2 mg. of desoxycorticosterone acetate daily for twenty-eight days completely inhibit the production of ketosteroids in the cells of the zona glomerulosa of the rat's adrenal cortex. Depletion of lipid from the zona glomerulosa is interpreted as a disuse atrophy produced by the exogenous supply of a hormone which can substitute for the normal products of this zone. A slight atrophy occurs also in the zona fasciculata following injection of desoxycorticosterone. This should probably be attributed to the suppression of secretion of the adrenocorticotropic hormone.

JACOBSEN, Buffalo.

CHANGES INDUCED IN THE ADRENAL CORTICAL ZONES BY OVARIAN HORMONES. DONALD J. KIMELDORF and A. L. SODERWALL, Endocrinology **41**:21 (July) 1947.

The injection of moderate amounts of estrogen into spayed female guinea pigs for a short time instigated hypertrophy of the adrenal cortex. The reticular zone of degenerate cells was greatly increased in size and the fascicular zone was reduced, while the glomerulosar zone was increased as compared with the controls. The suggestion is made that estrogen causes accelerated degeneration of the cortical cells. This, in turn, stimulates compensatory secretion of an adrenocorticotropic factor to produce hypertrophy of the secretory cortical cells. The injection of moderate amounts of progesterone for short periods caused an increase in relative adrenal weight and enlargement of the glomerulosar and reticularis zones. The life-maintaining properties of progesterone and the toxicity of estrogen are reflected in this study by the differential adrenal responses to injection of these two sex hormones.

JACOBSEN, Buffalo.

DETERMINATION OF THE RELATIVE ACTIVITIES OF ANTITHYROID COMPOUNDS IN MAN USING RADIOACTIVE IODINE. MALCOLM M. STANLEY and E. B. ASTWOOD, Endocrinology **41**:66 (July) 1947.

A new method is presented for assay of antithyroid drugs which depends on modification of a predictable pattern of accumulation of radioactive iodine by the thyroid gland as detected by serial counts with an externally placed Geiger-Müller counter. The results of assay of thirty-two compounds in 90 subjects are given.

JACOBSEN, Buffalo.

RESPONSE OF THE ALKALINE PHOSPHATASE OF THE ADRENAL CORTEX OF THE MOUSE TO ANDROGEN. HERBERT ELFTMAN, Endocrinology **41**:85 (July) 1947.

Alkaline phosphatase is present in notable concentration in the adrenal cortex of the adult male mouse. It is absent, or present only in traces, in that of the normal female.

Treatment with testosterone propionate results in the appearance of alkaline phosphatase in the adrenal cortex of the castrated male, the ovariectomized female and immature animals of both sexes.

The mobilization of cortical alkaline phosphatase by androgen provides another link in the chain of reactions associated with the normal function of androgens and of the adrenal cortex.

JACOBSEN, Buffalo.

THE DEVELOPMENT OF A REFRACTORY STATE TO THE ADRENOCORTICOTROPHIC HORMONE. EVELYN ANDERSON, ERNEST W. PAGE and CHOH HAO LI, Endocrinology **41**:105 (July) 1947.

After hypertension was established in rats, hypophysectomy caused a fall in blood pressure; administration of adrenocorticotropic hormone restored high pressure but the substance lost all effect after 23 days.

JACOBSEN, Buffalo.

THE QUANTITATIVE RECOVERY OF SYNTHETIC ESTROGENS FROM TISSUES OF BIRDS (GALLUS DOMESTICUS), THE RESPONSE OF THE BIRDS' TESTIS, COMB AND EPIDERMIS TO ESTROGEN AND OF HUMANS TO INGESTION OF TISSUES FROM TREATED BIRDS. S. BIRD, L. I. PUGSLEY and M. O. KLOTZ, Endocrinology **41**:282 (Oct.) 1947.

In the present communication observations on some of the events following ingestion of derivatives of diethylstilbestrol by male fowl are presented, particularly the distribution of ingested estrogens in the tissues, the effect on maleness, the rate of excretion and the events that may occur after ingestion of such tissues by human beings. An attempt to recover estrogenic materials from various tissues of treated birds showed that muscular tissues are low in potency, whereas tissues heavily infiltrated with lipids possess high potency. It appeared, therefore, that fractions of exogenous fat-soluble estrogens are taken up chiefly by lipid-containing tissues in preference to other tissues.

JACOBSEN, Buffalo.

PITUITARY AND CARBOHYDRATE METABOLISM OF THE BRAIN. M. REISS and D. S. REES, Endocrinology **41**:437 (Dec.) 1947.

The hexokinase activity of suspensions made from the gray matter of the brain was observed to be increased after hypophysectomy and adrenalectomy. The anaerobic glycolysis of slices of the gray matter of the brain was seen to be increased after hypophysectomy and could be reduced by treatment with adrenocorticotropic hormone.

After survey of these results, it can be concluded that, after hypophysectomy, a decisive disturbance develops in the carbohydrate household of the brain. The brain consumes and metabolizes an increased amount of sugar. Consequently, an exhaustion of sugar reserves takes place which might easily account for fits seen occasionally in hypophysectomized but otherwise untreated animals before their spontaneous death. Apparently, the brain burns more sugar after hypophysectomy.

JACOBSEN, Buffalo.

STUDIES ON THE BIOASSAY OF HORMONES: THE USE OF RADIOSODIUM FOR THE DETECTION OF SMALL QUANTITIES OF DESOXYCORTICOSTERONE. RALPH I. DORFMAN, ALBERT M. POTTS and MARY L. FEIL, Endocrinology **41**:464 (Dec.) 1947.

By the use of radiosodium it has been possible to devise a sensitive method for the bioassay of adrenal cortex steroids.

JACOBSEN, Buffalo.

METABOLISM OF THE STEROID HORMONES: STUDIES ON 17-KETOSTEROIDS AND ANDROGENS. RALPH I. DORFMAN, BENJAMIN N. HORWITT, REGINALD A. SHIPLEY, WILLIAM R. FISH and WILLIAM E. ABBOTT, Endocrinology **41**:470 (Dec.) 1947.

Even after the removal of the gonads and adrenal glands, both male and female monkeys continued to excrete about one-third the preoperative level of 17-ketosteroids and androgens. Since all the adrenalectomized and gonadectomized animals died of adrenal insufficiency, and since no adrenal tissue could be detected at autopsy, the possibility exists that there may be an extragonadal, extra-adrenal source of 17-ketosteroids and androgens.

JACOBSEN, Buffalo.

POTENTIATING EFFECTS OF ADRENAL CORTICAL EXTRACTS ON INSULIN-INDUCED ABNORMALITIES OF CHICK DEVELOPMENT. WALTER LANDAUER, Endocrinology **41**:489 (Dec.) 1947.

Adrenal cortex extract, injected into eggs either before the beginning of incubation or at one hundred and twenty hours of development, greatly delayed the growth of chicken embryos. This retardation of growth did not lead to the occurrence of malformations, although the hormone was injected at developmental periods during which insulin produces a high incidence of morphologic defects. It may be concluded that the effect of insulin is not mediated through a retardation of growth per se.

JACOBSEN, Buffalo.

EFFECTS OF VITAMIN A DEFICIENCY ON THYROID FUNCTION STUDIED WITH RADIOACTIVE IODINE. MORTIMER B. LIPSETT and RICHARD J. WINZLER, Endocrinology **41**:494 (Dec.) 1947.

The results of this study indicate that iodine metabolism is abnormal in the rat deficient in vitamin A.

JACOBSEN, Buffalo.

OVARIAN INFLUENCE ON THE RESPONSE OF THE ANTERIOR PITUITARY TO ESTROGENS. JAMES T. BRADBURY, Endocrinology **41**:501 (Dec.) 1947.

There are two theories of the action of sex hormones on the gonadotropic function of the pituitary. One theory is that sex hormones (estrogens and androgens) inhibit or suppress the gonadotropic function of the pituitary; the other is that the sex hormones stimulate the gland to elaborate and release increased quantities of gonadotropic hormone.

This communication summarizes a series of experiments designed to reinvestigate the effect of three to five days of estrogen treatment on the ovary and on the gonadotropic potency of the pituitary of the immature female rat. The earlier reports of a release of gonadotropin and ovarian stimulation are confirmed. In addition, evidence is presented that the ovary accelerates this action of the estrogen on the pituitary. Possible mechanisms whereby the ovary may participate in this action are discussed.

JACOBSEN, Buffalo.

STUDIES OF THYROID TOXICITY: I. A NUTRITIONAL FACTOR WHICH ALLEVIATES THE TOXICITY OF INGESTED THYROID SUBSTANCE. JOSEPH J. BETHEIL, V. D. WIEBELHAUS and HENRY A. LARDY, J. Nutrition **34**:431 (Oct.) 1947.

Betheil and his co-workers confirmed in these studies the presence in yeast of an antithyrotoxic factor and found liver to be a better source of this factor, which is not one of the known B vitamins. It is heat stable and under the experimental

conditions employed was not destroyed by autoclaving in acid or alkaline solution. Calcium pantothenate and inositol did not exert an antithyrotoxic effect when fed at high levels in a purified ration.

FREDEEN, Kansas City, Mo.

HISTOCHEMICAL DEMONSTRATION OF LIVER GLYCOGEN IN HUMAN DIABETIC ACIDOSIS BY LIVER BIOPSY. PHILIP K. BONDY and WALTER H. SHELDON, Proc. Soc. Exper. Biol. & Med. **65**:68 (May) 1947.

Inasmuch as careful histopathologic studies of the liver for glycogen in patients with diabetic acidosis are rare and incomplete, the authors availed themselves of the opportunity to obtain periodic biopsy specimens of liver from patients in such conditions. Photomicrographs of liver sections from 1 patient so studied showed severe glycogen depletion during the acidosis phase and restoration of glycogen after a few hours of therapy. These workers plan extension of biopsy studies of the liver on glycogen for correlation with the blood and clinical findings.

HANSEN, Galveston, Texas.

RATHKE'S CLEFT AND ITS CYSTS. M. L. BAYOUMI, Edinburgh M. J. **55**:745 (Dec.) 1948.

Cyst of Rathke's cleft (cyst of the craniobuccal pouch) was found in 26 (13 per cent) of 200 autopsies in the department of neuropathology, Royal Infirmary, Edinburgh. There was no evidence that these cysts were associated either with activity in the intermediate portion of the pituitary gland or with increased intracranial tension. This cyst can be differentiated from craniopharyngioma by careful histologic examination. Ciliated epithelial cells are invariably found in some part of the cyst wall on serial section.

MACDONALD, Pittsburgh.

HYPOTHYROIDISM WITH REPORT OF CASES. K. C. CHAUDHURI and N. G. MAJUMDAR, Indian J. Pediat. **14**:1 (Jan.) 1947.

Hypothyroidism in children is discussed from the standpoint of causation, pathologic changes, symptomatology and prognosis. Three cases are presented.

MCGUIGAN, Evanston, Ill.

THYROTOXICOSIS IN A CHILD AGED 2 YEARS 9 MONTHS. GERALD SLOT, Proc. Roy. Soc. Med. **40**:159 (Feb.) 1947.

The mother noticed about six months previous to the report that the child's eyes were becoming more prominent; otherwise the child had been normal. She did have pneumonia at 1 year of age. There was no family history of goiter. Results of physical examination and investigations and the treatment used are given in the report.

WILLIAMSON, New Orleans.

SPONTANEOUS HYPOGLYCEMIA IN CHILDHOOD. EMIL POLACEK, Ann. pædiat. **170**:1 (Jan.) 1948.

A case of spontaneous hypoglycemia on the basis of functional hyperinsulinism is described in a 3½ year old boy.

FROM THE AUTHOR'S SUMMARY.

EFFECT OF THE ADRENAL CORTEX ON THE SUGAR METABOLISM. L. BARTA, Ann. pædiat. **170**:189 (April) 1948.

It is shown in the introduction with 2 patients having thyroid disorders insensitive to treatment with thyroid extracts that healing may be recognized by the fact that the curves for the double dextrose tolerance test and for the galactose test become normal. It is fair to state, on the basis of cases in which no improvement ensued, that administration of desoxycorticosterone acetate (percorten®) may, as seen from the blood sugar curves, result in a definite Staub-Traugott effect in cases which did not display the effect formerly. In pituitary hypofunction treatment with adrenal cortex may bring about normal sugar metabolism as substantiated by the appearance of the Staub-Traugott effect and the normal galactose curve.

Finally, a rare case of diabetes is reported in which the carbohydrate metabolism underwent improvement following the administration of adrenal cortex. In this connection the relation of von Gierke's disease (glycogenosis) to the dysfunction of the pituitary is pointed out. It is assumed that the pituitary may be responsible for pathologic glycogen storage by an effect on the adrenal cortex.

FROM THE AUTHOR'S SUMMARY.

INFLUENCE OF DESOXYCORTICOSTERONE ACETATE ON DISTURBANCES IN HEPATIC FUNCTION IN INFANCY. L. BARTA, Ann. pædiat. **171**:158 (Sept.) 1948.

The administration of adrenal cortex preparations in cases of atrophy produces a restoration of the pathologic sugar metabolism to normal. In 1 case in which this therapy was not completely successful, besides desoxycorticosterone acetate (percorten®), an amino acid preparation and potassium were given, which caused the glucose and the galactose metabolism to become normal again.

It is my opinion that the pathologic glucose and galactose metabolism is caused by hepatic deficiency. The disturbed hepatic function has to be considered a part of a general cell dysfunction. It is probable that the cell dysfunction is accompanied with an exchange of bases: Potassium is replaced in the cell by sodium.

Toxicosis is an acute form of disturbed mineral metabolism, while atrophy is a chronic one. I propose to augment the treatment with adrenal cortex in both forms by administration of potassium.

FROM THE AUTHOR'S SUMMARY.

SUGAR TOLERANCE TESTS IN ENDOCRINE DYSFUNCTIONS. L. BARTA, Paediat. danub. **3**:233 (May) 1948.

In 35 cases of endocrine dysfunction the peculiarities of the blood sugar curves were studied. In 3 patients the epinephrine tolerance curve was pathologic. In the patients with myxedema the epinephrine curves were steep though normal, but the insulin tolerance curves were pathologically flat in 50 per cent of the patients with nanosoma and myxedema and the blood sugar value fell to less than 45 mg. per hundred cubic centimeters. In more than 50 per cent (in 14 of 26 patients) the Staub-Traugott effect in the double dextrose tolerance test was absent. An absent Staub-Traugott effect with a flat galactose curve is a sign of hypothyroidism. Pathologically high galactose curves associated with the failure of the Staub-Traugott effect point to a disorder of glycogen storage which is observed with pituitary nanosoma and hyperthyroidism. In patients with endocrine dysfunction the adrenocortical hormone influences the results of the double dextrose tolerance test favorably. On the basis of the outcome in these patients the diagnostic importance of the dextrose tolerance test is stressed.

FROM THE AUTHOR'S SUMMARY.

ADRENOCORTICAL HYPOFUNCTION (ADDISON'S DISEASE) IN A CHILD AS A RESULT OF CIRRHOSIS OF ADRENAL GLANDS. HORST BICKEL and OTTO STAMM, Helvet. paediat. acta **3**:53 (Feb.) 1948.

A description is given of a case of typical adrenocortical hypofunction (Addison's disease) in a girl aged 7 years. The autopsy showed the cause to be adrenal cirrhosis and severe adrenal atrophy, probably the last stage of a toxic adrenal infection. The previous history, the course of the disease and the results of the autopsy and histologic examination make it seem likely that this adrenal infection followed closely on and was caused by a severe attack of impetigo contagiosa.

FROM THE AUTHORS' SUMMARY.

LYMPHOCYTOSIS AND THYMIC HYPERPLASIA. E. GORTER, Nederl. tijdschr. v. geneesk. **92**:1898 (June 26) 1948.

A boy, aged 1 year, whose illness was diagnosed as bronchopneumonia, showed on roentgenographic examination a shadow in the upper mediastinum. At first, this shadow seemed to be due to enlarged lymph nodes, but after three months, as a notch became visible at the crossing of the cardiac shadows, hyperplasia of the thymus was considered probable. The tuberculin reactions were all negative. There was anemia (hemoglobin concentration, 9.2 Gm. per hundred cubic centimeters, with 4,300,000 erythrocytes per cubic millimeter) with 76.5 per cent lymphocytes in a total number of 7,600 leukocytes per cubic millimeter. The bone marrow was normal. A total of 8 roentgen treatments (200 r each) and an iron preparation by mouth were given. The leukocytes, which were increased before irradiation to 17,000 per cubic millimeter, with 63 per cent lymphocytes, decreased quickly during the treatment, while the lymphocytosis disappeared. Seven weeks after the irradiation treatments were stopped, the shadow in the mediastinum had disappeared and the general condition of the boy was excellent. In this case the differential diagnosis between leukemia, thymic tumor and acute and chronic infectious lymphocytosis (Smith) were discussed.

VAN CREVELD, Amsterdam, Netherlands.

Skin Diseases; Allergy

PREVENTION BY SODIUM OF ARTERITIS IN THE EXPERIMENTAL ALLERGIC STATE. CLEMENT J. SULLIVAN, THOMAS W. PARKER and RUSSELL W. HIBBERT, Proc. Soc. Exper. Biol. & Med. **67**:508 (April) 1948.

Twenty albino rabbits were given intravenous injections of horse serum, first, 10 cc. per kilogram of body weight, then sixteen days later 1 cc. per animal, and in six days they were again given 10 cc. per kilogram of body weight. Thirty-one days previously, 3 of the animals were given paraaminobenzoic acid by mouth, and eight days before the injection of serum sodium salicylate, 0.2 Gm. per kilogram of body weight, was given daily subcutaneously to 12 animals, with the first dose intravenously to 2. Three animals received only the horse serum. All animals were killed, 1 after completion of the injections of horse serum. The control animals and those fed the paraaminobenzoic acid had arterial lesions and circulating antibodies at the end of the experiment. The animals given sodium salicylate subcutaneously showed no arteritis, but they did produce circulating antibodies. However, the animals first given sodium salicylate intravenously had arteritis and glomerular changes but circulating antibody was scarcely detectable. The authors are of the opinion that lesions do not develop because there is no antigen-antibody reaction, as salicylate prevents antigen from uniting with the tissue cells.

HANSEN, Galveston, Texas.

INTRAVENOUS ETHYL ALCOHOL IN THE TREATMENT OF STATUS ASTHMATICUS IN CHILDREN. H. L. BARAL and S. PEDVIS, Canad. M. A. J. **59**:410 (Nov.) 1948.

The use of ethyl alcohol intravenously in 3 children aged 2 to 10 years is described. In all the children, epinephrine had failed to relieve symptoms. The dose used was 40 cc. per kilogram of body weight of a 5 per cent solution of alcohol in 5 per cent glucose solution in isotonic sodium chloride solution. In all the children, relief was complete and without untoward reactions. A brief summary of the physiologic action of alcohol and a short review of the literature are included.

McGUIGAN, Evanston, Ill.

CONGENITAL LYMPHOEDEMA (MILROY'S DISEASE). N. G. MOJUMDAR, Indian J. Pediat. **15**:135 (July) 1948.

A case of familial hereditary edema (Milroy's disease) is reported briefly. No familial history could be obtained.

McGUIGAN, Evanston, Ill.

SCLEREMA. DONALD PATERSON, Proc. Roy. Soc. Med. **40**:160 (Feb.) 1947.

A case of sclerema is reported in a boy 11 months of age.

WILLIAMSON, New Orleans.

CALCINOSIS UNIVERSALIS. DONALD PATERSON, Proc. Roy. Soc. Med. **40**:160 (Feb.) 1947.

Calcinosis universalis is reported in a patient 3½ years of age, who was well until she was 17 months old, when she stopped crawling and objected to her limbs being moved. At the age of 2 years abscesses developed on the buttocks, and a few months later hard lumps were noticed in the skin around the lower ribs.

The results of physical examination, roentgenologic study and biochemical determinations, the blood count and biopsy report are given in the account.

WILLIAMSON, New Orleans.

ERYTHEMA ANNULARE (LEHNDORFF-LEINER) WITHOUT OTHER RHEUMATIC MANIFESTATIONS. WALTER WINKLER, Ann. pædiat. **168**:303 (June) 1947.

A case of erythema annulare (Lehndorff-Leiner) is described in which no other manifestations of rheumatic disease could be discovered. The illness cleared up after tonsillectomy but could be repeatedly reproduced by a streptococcic autovaccine cultured from the tonsils and from swabs of the throat. Whenever these spontaneous relapses occurred, hemolytic streptococci or Streptococcus viridans could be found in the throat; they were, however, absent during the intervals. The fact that there were antibodies present against these bacilli was demonstrated by the positive reaction to the Prausnitz-Küstner test. The author attempts to make use of these observations with regard to true rheumatism.

FROM THE AUTHOR'S SUMMARY.

PUBERTAS PRECOX ACCOMPANIED WITH NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE). L. BARTA, Ann. pædiat. **170**:15 (Jan.) 1948.

A boy 9 years of age with neurofibromatosis and pubertas precox is reported on. The relation between the two conditions is pointed out. There were few

symptoms from the neurofibromatosis. A biopsy specimen of a piece of tissue from the forearm which was clinically atypical clarified the diagnosis.

FROM THE AUTHOR'S SUMMARY.

ERYSIPELOTHRIX RHUSIOPATHIAE INFECTION IN CHILDREN. G. GASPARI, Clin. Pediat. **31**:231 (April) 1949.

Two cases of "swine erysipelas" in children are reported. The disease was characterized by a generalized reaction and by skin lesions. The disease responded rapidly and favorably to penicillin.

HIGGINS, Boston.

LINOLEIC ACID IN EXUDATIVE DIATHESIS IN NURSLINGS. I. LAX, Policlinico inf. **15**:324 (July) 1947.

After administration of small quantities of pure linoleic acid, the author observed a veritable amelioration of clinical manifestations of the disease and a return to normal values of blood iodine count.

The author attributes these results to the antiallergic activity of the linoleic acid.

FROM THE AUTHOR'S SUMMARY.

VALUE OF DIAGNOSTIC SKIN TESTS IN ALLERGIES IN BRONCHIAL ASTHMA. MARIO SCARZELLA and ALDO SOLA, Policlinico inf. **16**:217 (March) 1948.

The authors studied skin reactions to protein in children with asthma and hay fever (scratch tests). Mostly they found an anaphylaxis to pollens; often this was associated with an anaphylaxis to epidermic derivatives and alimentary proteins.

Desensitization treatment gave good results in the asthma due to pollen and that caused by epidermic derivatives. The results obtained in the alimentary asthma were, for the most part, unsatisfactory.

FROM THE AUTHORS' SUMMARY.

CHANGES IN THE BLOOD PICTURE IN INFANTS WITH ECZEMA AND IN INFANTS ARTIFICIALLY SENSITIZED TO EGG WHITE. H. BRIEGER, Ztschr. f. Kinderh. **65**:155, 1947.

The author set out to study the changes in the blood picture in normal children, in children with eczema sensitive to egg white and in infants given intracutaneous injections of serum from infants with eczema. Intracutaneous injections of egg white in normal children provoked leukocytosis identical to the changes found by the author after injections of sodium chloride solution. In infants with eczema sensitive to egg white the leukocytic response was more pronounced. Whereas serum from infants with eczema produced leukocytosis in normal infants when given in intracutaneous injections, injections of egg white in artificially sensitized infants produced leukopenia. The author tries to explain these manifestations by disturbances in the balance of the autonomic nervous system of the periphery and the abdomen, leading at times to shocklike reactions with vasoconstriction of the peripheral and vasodilatation of the splanchnic blood vessels.

GLASER, Chicago.

UNUSUAL LOSS OF HAIR FOLLOWING ROENTGEN IRRADIATION. C. GEFFERTH, Paediat. danub. **3**:124 (March) 1948.

Irradiation of the brain of feebleminded children is a common practice. Extensive loss of hair was observed in several instances, although the doses administered were much below those used for epilation. The first series was given hard rays of 60 r on different parts of the skull in four to five sittings. Six weeks later the same quantity was administered with a similar technic. Three months later, a third series was given; in this the dose administered was 90 r to each sector of the skull.

Another child with cervical lymphadenitis lost his hair, although no direct rays fell on the head. This patient received 265 r first and then five days later 282 r. Some weeks afterward, hydrocephalus developed. It is felt that the cause of the unusual loss of hair might be in the organism itself, certain characteristics being activated by the irradiation, or the disturbance may be due to the disturbed hormonal equilibrium. It is, however, possible that some abnormal reaction of the nervous system was responsible for the unusual phenomenon.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF IMPETIGO. J. TAMÁSI, Paediat. danub. **3**:160 (March) 1948.

The different forms of impetigo are much commoner in infants and children than in adults. This is due partly to the sensitivity of the skin in childhood and partly to low resistance to infections.

Local treatment consists in removal of the crusts to make the lesions accessible to antiseptics and in application of these agents. In general treatment, sulfonamides may be used and, in extensive cases complicated by furunculosis, transfusions, homologous serum and penicillin. To prevent spread by the patient's fingers, cuffs may be applied to the arms for the entire duration of the treatment. Bathing should not be allowed.

Forty-two infants and children with impetiginous disorders were treated. A 10 per cent ointment of iodochlorohydroxyquinoline N. F. (vioform®) and zinc was observed to be the most effective for local application. Sulfathiazole was given orally in doses of 0.2 Gm. per kilogram of body weight every day for three days to those under 3 years and in doses of 3 to 4 Gm. per day to those above this age. In addition to this, homologous serum was also administered, 20 cc. three times a day every other day to infants and double doses to older children. The crusts soon disappeared, and healing was complete in five to seven days. There were no relapses.

FROM THE AUTHOR'S SUMMARY.

NEUROFIBROMATOSIS AND HORMONAL DYSFUNCTION. L. BARTA, Paediat. danub. **3**:310 (June) 1948.

Two cases are reported in both of which grave endocrine disturbances associated with neurofibromatosis occurred. In the first child nanosomia, hypogenitalism and moderate obesity were present. The double dextrose tolerance test yielded no Staub-Traugott effect. Dextrose tolerance following a dose of insulin revealed a decreased counterregulation, as after two and a half hours the sugar level in the blood was still as low as 40 mg. per hundred cubic centimeters. Following administration of epinephrine, there was only a slight rise in the blood sugar. In the concentration test the excretion of only half the water given within four hours is explained by a decreased production of diuretic hormone or by an increased antidiuretic effect. The rate of diuresis could be somewhat ameliorated

but not normalized by doses of thyroxin. Posterior pituitary injection U.S.P. (pituitrin®) had a pronounced effect. The specific gravity of the urine, which after ingestion of water without drugs rose to 1.029 during the concentration period, reached only 1.011 when desoxycorticosterone acetate was given in addition. This phenomenon may be due to the increase of salt retention caused by cortical hormone. Encephalography revealed a large hydrocephalus. It is supposed that a close correlation existed between the disturbances of the central nervous system and the neurofibromatosis.

The second child presented premature puberty of cerebral type and had excruciating headaches. There was discoloration of the temporal portions of both retinas. A causal relation between neurofibromatosis and endocrine dysfunction was also supposed to exist in this case.

It is assumed that in cases in which endocrine dysfunctions associated with neurofibromatosis occur the symptoms arise in connection with neurofibromatotic foci in the diencephalon or in consequence of secondary pressure exerted on this portion of the brain. In the first case the pressure was probably exerted by the hydrocephalus, which developed in consequence of the neurofibromatosis.

FROM THE AUTHOR'S SUMMARY.

TREATMENT AND PROGNOSIS OF ASTHMA IN CHILDHOOD. E. B. SALÉN, Svenska läk.-tidning. **43**:18 (Jan. 4) 1946.

A report is presented on a follow-up study of children admitted to a hospital for asthmatic patients and there treated with specific and unspecific desensitizing and anti-infectious measures. Of the 99 children 85 were reexamined, and of these 74 were quite free from symptoms during the six months to seven years which had elapsed from their discharge from the hospital. Acute catarrhal infections played a considerable part in the development of asthmatic attacks. Dust allergen is a frequent cause of asthma in childhood.

WALLGREN, Stockholm, Sweden.

RHEUMATIC ERYTHEMA NODOSUM IN CHILDREN. OLOF GERTZÉN, Svenska läk.-tidning. **43**:220 (Jan. 25) 1946.

A girl, 4½ years old, who had valvular disease after rheumatic fever, became ill with pains in her legs, erythema nodosum and signs of active endocarditis. There had been no preceding acute infection nor had any sulfonamide drugs been given. Before the illness she had had a positive reaction to tuberculin after BCG vaccination, and there was no increase in her tuberculin sensitivity concomitant with the eruption of erythema nodosum. The sedimentation rate was strongly increased. Roentgenologic study of the lungs showed no abnormality and no tubercle bacilli were yielded on gastric lavage.

WALLGREN, Stockholm, Sweden.

DERMATITIS HERPETIFORMIS (DUHRING) IN NEWBORN INFANTS. G. ASBOE HANSEN, Ugesk. f. læger. **109**:222 (Feb. 27) 1947.

Two cases are reported of symmetrically localized papulovesicular-pustular dermatitis most pronounced on the legs, with eosinophilia and keratosic healing.

WALLGREN, Stockholm, Sweden.

TREATMENT OF ALLERGIC DISEASES IN CHILDREN WITH DIPHENHYDRAMINE HYDROCHLORIDE (BENADRYL®). E. WINGE FLENSBORG, Ugesk. f. læger **109**:639 (Oct. 9) 1947.

Twenty-seven children with various allergic diseases were treated with diphenhydramine hydrochloride (benadryl®). The effect of the drug was good in urticaria and hay fever, uncertain in vasomotor rhinitis and absent in asthma. In 2 of 3 children with idiosyncrasy to cow's milk benadryl® prevented the reaction produced by ingestion of the substance; in the third child no effect was demonstrable.

WALLGREN, Stockholm, Sweden.

Miscellaneous

A SURVEY OF THE ACCURACY OF CHEMICAL ANALYSES IN CLINICAL LABORATORIES. F. W. SUNDERMAN, Am. J. Clin. Path. **17**:853 (Nov.) 1947.

Fifty-nine hospital laboratories were sent known specimens for the determination of hemoglobin, glucose, chloride, total protein, albumin, calcium and urea. Only 30 to 50 per cent of the laboratories reported values in the range covered by the accuracy of the method; the rest were completely unsatisfactory. No one single laboratory reported satisfactory values for each of the seven determinations. For example, a solution containing 6.6 mg. of calcium per hundred cubic centimeters brought forth values ranging from 3 to 13 mg. per hundred cubic centimeters; in only 14 of the 55 laboratories reporting did the values fall within the expected range of 6.1 to 7.1 mg. per hundred cubic centimeters. A solution of 60 mg. of glucose per hundred cubic centimeters produced values ranging from 40 to 120 mg. per hundred cubic centimeters; with an allowed range of ± 10 mg. per hundred cubic centimeters, only half the laboratories reported satisfactorily. When questioned concerning the possible reasons for such obviously unreliable work, the various laboratory directors gave poor training, an inadequate number of technicians and lack of understanding between the laboratory pathologist and the staff as the principal causes. FORBES, St. Louis.

A CLINICAL EVALUATION IN CHILDREN OF THE TOXICITY AND EFFICACY OF CARONAMIDE (4′-CARBOXYPHENYLMETHANESULFONANILIDE) FOR THE COMPETITIVE INHIBITION OF PENICILLIN EXCRETION. MILTON RAPOPORT, F. BRUCE CORNEAL, KARL H. BEYER and W. F. VERWEY, Am. J. M. Sc. **215**:514 May) 1948.

When tested in children, the oral administration of carinamide at a dose of 0.2 Gm. per kilogram of body weight per day, together with penicillin, increased the antibiotic plasma concentration 1.8 to 2.8 fold over the control values when penicillin was administered alone. When the dosage of carinamide was increased to 0.4 Gm. per kilogram of body weight per day, the penicillin plasma concentration was increased 2.8 to 14.5 fold over the control figures.

The authors report no instance of toxicity in these patients that warranted discontinuance of treatment with carinamide when the compound was administered in oral doses of 0.1 to 0.4 Gm. per kilogram of body weight per day over a period of one or two weeks. Although there were two urinary specimens that contained crystals of the drug and three instances of rash, in which no 2 cases were similar

in appearance or distribution, these did not require special attention. Two of the rashes cleared up during continued administration of the drug and the third appeared twenty-four hours after use of the drug had ceased. There were 3 cases in which one or more isolated instances of "pentosuria" were found, and these were associated with a pharyngitis, smallpox vaccination or the rash that appeared after use of the drug had been stopped.

By means of renal function tests performed before and at the end of the coadministration of penicillin and carinamide, it was ascertained that the latter compound did not influence irreversibly glomerular filtration, renal plasma flow or tubular reabsorption of paraaminohippuric acid or glucose. HENSKE, Omaha.

THE CLINICAL USE OF PENICILLIN IN OIL AND BEESWAX IN PEDIATRIC PRACTICE. FREDERICK M. ADAMS and ELIZABETH G. FISHER, Bull. Johns Hopkins Hosp. **82**:373 (March) 1948.

Penicillin in oil and white wax was used in 100 cases of pneumonia, with good results in 92 cases. It was used in 80 cases of miscellaneous infections, with good results in 73 cases. The penicillin blood levels with this method of injection were extremely variable. There were no allergic reactions, and no instances of acquired sensitivity to penicillin or to the vehicle of peanut oil and white wax could be demonstrated by subsequent injection of these products two to four months later. LYTTLE, Los Angeles.

DR. ISAAC ABT AND HIS CONTRIBUTION TO PEDIATRICS. A. LEVINSON, Illinois M. J. **93**:6 (Jan.) 1948.

This article is a tribute to Dr. Abt and gives a short description of his contribution to the field of pediatrics as a writer, teacher and practicing pediatrician.

BARBOUR, Peoria, Ill.

FATAL PEDICULICIDE POISONING (ABSORPTION THROUGH SCALP). BENEDICT SKITARELIC, J. A. M. A. **134**:1297 (Aug. 16) 1947.

A 2 year old child who had been treated for a month with a pediculicide called kil-ve® (a preparation of fishberry and sabadilla seed, extracted in 72 per cent isopropyl alcohol and 27.5 per cent water) was well at 4 p.m. but was found dead at 7 p.m. At autopsy the only significant observations were in the brain, the liver and the lungs. The presence of picrotoxin and veratrine was revealed in the brain and the liver but not in the contents of the stomach. The concentration in the brain was sufficient to have caused death. Fatal poisoning had apparently occurred by absorption through the skin. BAIRD, Wauwatosa, Wis.

CARONAMIDE FOR INCREASING PENICILLIN PLASMA CONCENTRATIONS IN MAN. J. WILLIAM CROSSON, WILLIAM P. BOGER, CHRISTOPHER C. SHAW and A. KATHRINE MILLER, J. A. M. A. **134**:1528 (Aug. 30) 1947.

Carinamide is an orally effective compound of low toxicity capable of producing a reversible inhibition in the excretion of penicillin by the renal tubules. Doses of 2 Gm. of carinamide every four hours, or 1.5 Gm. every three hours, were demonstrated to produce an increase in blood levels of penicillin of from two to seven times when penicillin was administered orally or intramuscularly. Results

with penicillin administered in white wax and oil were inconclusive, and further studies are required to demonstrate the effect of carinamide. No evidence of toxicity was noted in the small series of patients presented.

BAIRD, Wauwatosa, Wis.

POISONING DUE TO TINCTURE OF RHUS TOXICODENDRON. HARRY LOWENBURG JR., J. A. M. A. **135**:91 (Sept. 13) 1947.

An 11 year old boy with a long history of pyelonephritis due to congenital strictures at the ureterovesicular junctions was hospitalized because of an elevation in temperature to 105 F., which later rose to 109.2 F., associated with chills and later a generalized convulsion. His condition was critical for 48 hours. Neurologic examination revealed paralysis of upward gaze and near convergence plus weakness of the left leg. These findings, with the occurrence of hematemesis, led to further questioning of the family. It was found that the boy had been taking increasing doses of tincture of Rhus toxicodendron. On the four days just prior to admission he had taken 45, 55, 57 and 57 drops. The maximum recommended dose for an adult is 5 drops three times daily. It was the author's opinion that this drug was responsible for the gastritis and the central nervous system findings. Recovery was eventually complete.

BAIRD, Wauwatosa, Wis.

THE USE OF ANTIBIOTICS. PERRIN H. LONG, CAROLINE A. CHANDLER, ELEANOR A. BLISS, MORTON S. BRYER and EMANUEL B. SCHOENBACH, J. A. M. A. **141**:315 (Oct. 1) 1949.

The useful antibiotics and the infections against which they are effective are discussed and tabulated.

KIMBALL, Evanston, Ill.

THE EFFECTS OF CYTOCHROME C ON ANOXIC AND CYANIDE-POISONED RATS. H. O. MICHEL and I. H. SCHEINBERG, J. Biol. Chem. **169**:277 (July) 1947.

The authors failed to confirm the results of other workers with regard to the action of cytochrome C in mitigating the physiologic effects of anoxia. In the experiments herein reported, cyotchrome C was injected intravenously into adult rats as a 1 per cent aqueous solution in doses ranging from 20 to 50 mg. per kilogram of body weight. Pretreatment with cytochrome C failed to prevent the rise in blood lactic acid or the fall in the easily hydrolyzable phosphorus content of the kidney and heart (the latter being a measure of adenosine triphosphate and diphosphate content) in the rat subjected to cyanide poisoning. Similar observations were noted in rats exposed to an atmosphere containing 3.9 per cent oxygen for five minutes; again cytochrome C failed to prevent the changes in blood lactic acid and the easily hydrolyzable phosphorus content of the organs. Further, administration of cytochrome C had no effect on the survival time of rats exposed to an atmosphere of 2.8 per cent oxygen. It was possible to recover about 5 per cent of the injected dose of cytochrome C (5.7 mg. per kilogram of body weight) in the urine over a four hour period.

FORBES, St. Louis.

THE BABY'S DIAPER WITH SUGGESTIONS FOR ITS IMPROVEMENT. CHARLES F. MCKHANN and GEORGE BRICMONT, J. Pediat. **34**:131 (Feb.) 1949.

The improvement is a curved waterproof diaper envelop that contains a disposable pad of absorbent material. Only a small area of this pad is exposed to the infant's excreta, and this part of the pad is held away from the baby's skin. The device eliminates diaper rash.

MACDONALD, Pittsburgh.

TESTS FOR THE CHRONIC TOXICITY OF PROPYLENE GLYCOL AND TRIETHYLENE GLYCOL ON MONKEYS AND RATS BY VAPOR INHALATION AND ORAL ADMINISTRATION. O. H. ROBERTSON, CLAYTON G. LOOSLI, THEODORE T. PUCK, HENRY WISE, HENRY M. LEMON and WILLIAM LESTER JR., J. Pharmacol. & Exper. Therap. **91**:52 (Sept.) 1947.

The senior author, and other of his associates, had already shown that the triethylene glycol and propylene glycol were "highly germicidal for air-borne bacteria and viruses" and that they were essentially nontoxic to animals. The objective of the present investigation was to determine whether the vapors of these chemicals were toxic to a series of animals (monkeys and rats) exposed continuously to high concentrations for periods of twelve to eighteen months. Equal numbers of control animals were maintained under similar physical conditions. Another series was fed propylene glycol and triethylene glycol in doses up to seven hundred times the amount that could be absorbed from breathing air saturated with substances. In neither series was there evidence of injury to the animals as shown by the growth, blood counts, urine and results of renal function tests. The autopsy observations also revealed no abnormality. The authors conclude that exposure to the saturated vapors of these agents for months at a time is completely harmless. This procedure is certainly promising for trial in pediatric hospital wards.

PILCHER, Cleveland.

CERTAIN PHARMACOLOGIC PROPERTIES OF 4'-CARBOXYPHENYLMETHANESULFONANILIDE (CARONAMIDE), INCLUDING ITS EFFECT ON THE RENAL CLEARANCE OF COMPOUNDS OTHER THAN PENICILLIN. KARL H. BEYER, HORACE F. RUSSO, ELIZABETH A. PATCH, ELIZABETH K. TILLSON and GRACE SHANER, J. Pharmacol. & Exper. Therap. **91**:272 (Nov.) 1947.

Other work has shown that carinamide increases the blood level of penicillin by decreasing the renal excretion of penicillin. Through experiments on dogs, the present paper shows that "the inhibitory effect of caronamide is on a renal tubular excretory transport mechanism. . . ."

Carinamide did not influence other renal functions. Concentrations of the drug that suppressed the tubular excretion of penicillin completely did not influence significantly the heart or the respiratory rate, the systemic blood pressure or the renal volume.

PILCHER, Cleveland.

MOBILIZING OUR NATIONWIDE RESOURCES FOR SERVICE TO THE HANDICAPPED. LAWRENCE J. LINCK, J. Speech Disorders **12**:11, 1947.

This article is the address of the executive secretary of the National Society for Crippled Children and Adults, Inc., to the annual convention of the American Speech Correction Association, giving the general principles of the national society in its cooperation with general clinical and other services for handicapped children in this country and its efforts to develop more adequate ones.

PALMER, Wichita, Kan.

STREPTOMYCIN: ITS PRESENT USES. DONALD R. NICHOLS, Minnesota Med. **30**:1263 (Dec.) 1947.

The author has reviewed thoroughly the effectiveness of streptomycin in controlling certain infections in patients at the Division of Medicine of the Mayo Clinic, Rochester, Minn. He summarizes his work at this time by stating that

streptomycin appears to be definitely superior to other available chemotherapeutic agents in the treatment of certain diseases. These diseases include tularemia, meningitis caused by Hemophilus influenzae, bacteremia caused by susceptible organisms, uncomplicated infections of the urinary tract caused by certain organisms, pneumonia caused by Klebsiella pneumoniae or H. influenzae and some forms of tuberculosis. Certain toxic manifestations are occasionally encountered when streptomycin is administered to patients.

STOESSER, Minneapolis.

A FAMILY OUTBREAK OF LEAD POISONING FROM STORAGE BATTERY CASINGS. DAVID SPIZER, New Orleans M. & S. J. **100**:278 (Dec.) 1947.

The source of 4 cases of lead poisoning in a family of 6 was found to be storage battery casings used as fuel in a stove in the children's room. One of the patients died, and the other 3 had evidence of lead encephalopathy.

McGUIGAN, Evanston, Ill.

USE OF ANTIBIOTICS IN PEDIATRICS. GEORGE W. SALMON, New Orleans M. & S. J. **100**:361 (Feb.) 1948.

Various cases in which treatment with penicillin was given are described as illustrations of the use of antibiotic drugs in pediatrics.

McGUIGAN, Evanston, Ill.

BAL IN THE TREATMENT OF ARSENIC INGESTION OF CHILDREN. NORMAN C. WOODY and JOHN T. KOMETANI, Pediatrics **1**:372 (March) 1948.

Experiences with the use of BAL (2,3-dimercaptopropanol) for 42 children who had ingested arsenic were reviewed. This was done to determine the frequency, severity and types of reactions caused by BAL, to ascertain whether criteria for safety were met and to derive suggested dosage schedules for use in children. The problems posed by accidental ingestion of arsenic and the background of experimental and clinical experiences with BAL were discussed.

After contrasting effects of BAL in infants and adults, a brief table of dosage schedules to be used in treatment of arsenic ingestion in infants and children could be arranged. Then after comparison of the results observed in these 42 children with those following earlier methods of therapy, it was possible to conclude that BAL is an effective, safe and useful chemical antidote for children who ingested arsenic. A plan of treatment employing BAL is presented.

FROM THE AUTHORS' SUMMARY.

JET INJECTION IN PEDIATRIC PRACTICE. JAMES G. HUGHES, ROBERT G. JORDAN and FONTAINE S. HILL, Pediatrics **3**:801 (June) 1949.

The technic of jet injection is described. It represents the first fundamental change in the basic principles of injection in almost one hundred years. The method is relatively painless, is practically innocuous to tissue and has technical simplicity. Information is presented dealing with depth of penetration of substances injected, pain response of children, local effects on tissues, blood levels of penicillin and of streptomycin given by jet injection and clinical response of patients given penicillin by this technic.

Discussions are included concerning the need for chemical inertness of the metal used in metapule, viscosity of material to be injected and the possibility of inadvertent intravenous injection.

The proper instrument for children under 10 years of age seems to be one with 75 pounds (34 Kg.) spring pressure and for children 10 years of age or older one with 100 pounds (45 Kg.) of spring pressure. With these strengths it has consistently been possible to secure intramuscular injections in the deltoid and triceps areas and subcutaneous injections in the lateral thigh area. Injections over large veins should obviously be avoided.

Jet injection offers promise in the field of pediatrics chiefly because of its relative painlessness. It may prove of value in mass immunizations, not only because of pain prevention and technical simplicity but also because the transmission of viral agents from one subject to another by contaminated needles would be avoided. Further investigations are indicated, for the relief of pain is one of the foremost functions of a physician.

FROM THE AUTHORS' SUMMARY.

A NEW REPOSITORY PENICILLIN (A FORM OF AQUEOUS PENICILLIN G PROCAINE) IN INFANTS AND CHILDREN. HORACE M. GEZON, DUKE CHO CHOY, DAVID T. HELLYER, WILLIAM H. SMITH and FRED L. STRICKER, Pediatrics **4**:9 (July) 1949.

Eighty-two children with a variety of infectious diseases were treated with a daily injection of a new repository penicillin, aqueous procaine penicillin G. Clinical success was obtained in 68 of 75 patients. In 1 the results were considered fair, in 3 poor and in 3 unknown.

Thirty-five patients had beta hemolytic streptococcus and 10 pneumococcus isolated from the nose or throat. Bacteriologic success was obtained in all streptococcic infections but in only 6 of 10 pneumococcic infections. All the streptococci were sensitive to penicillin when tested by in vitro methods.

Penicillin serum levels with a mean maximum of approximately 2 units per cubic centimeter were observed at two hours and a mean minimum of approximately 0.063 unit per cubic centimeter at twenty-four hours. The curve for intermediate values approximated a normal curve.

FROM THE AUTHORS' SUMMARY.

STUDIES OF PENICILLIN IN PEDIATRICS. B. M. KAGAN, L. KISHNER, A. MILZER and M. SACKS, Pediatrics **4**:79 (July) 1949.

A study was made of the relative degrees of in vitro sensitivity to penicillin of various pathogenic bacteria. Different strains vary considerably in their sensitivity to penicillin. The concentrations of penicillin obtained in the serum following varying dosages per unit of body weight in infants and children when given in the following forms are reported: crystalline sodium penicillin G in saline solution given intramuscularly; the same compound of penicillin in gelatin capsules and in suppositories of theobroma oil and white wax given rectally; crystalline sodium penicillin G in sesame oil give intramuscularly, and crystalline potassium penicillin G in a new type Romansky formula given intramuscularly. The last preparation, when given in doses of 4,000 units per pound (0.5 Kg.), maintained serum penicillin concentrations twenty-four hours after administration in 94 per cent of cases which were above the minimum concentration required to inhibit most strains of alpha and beta hemolytic streptococci and of Klebsiella pneumoniae, and the serum concentrations obtained with this preparation twelve hours after administration were equal to or above the minimum concentration required to inhibit most strains of hemolytic Staphylococcus aureus and of Meningococcus.

FROM THE AUTHORS' SUMMARY.

A Method for Producing Sustained High Penicillin Levels in the Blood. F. H. King, S. S. Schneierson, M. L. Sussman, H. D. Janowitz and L. Blum, Proc. Soc. Exper. Biol. & Med. **66**:548 (Dec.) 1947.

One to two million units of crystalline penicillin was dissolved in 5 cc. of distilled water. The solution was injected rapidly into the antecubital vein through a 15 gage needle, the injection being completed within five seconds. No clinical or electrocardiographic abnormalities resulted following this rapid administration of penicillin. In the 3 patients, penicillin was injected before and after the administration of carinamide (4′-carboxyphenylmethansulfonanalide), 4 Gm. being given orally every three hours day and night for twenty-four hours, starting before the antibiotic was administered. There was a progressive fall in the blood penicillin level during the three hour interval, the most precipitous drop occurring thirty minutes after the injection of penicillin. At the end of the three hour period, the blood level of penicillin in the patients receiving carinamide was five to fifteen times higher than in the same patients without carinamide. The intra-aortic blood levels were much higher, decidedly, than the levels of penicillin in the peripheral blood. The authors suggest that such a technic may be useful for the rapid sterilization of the vegetations of bacterial endocarditis.

Hansen, Galveston, Texas.

Aluminum Penicillin in Mouse Protection Tests. Roger D. Reid, Proc. Soc. Exper. Biol. & Med. **66**:650 (Dec.) 1947.

The amorphous aluminum salt of penicillin was prepared. This substance is highly insoluble in water. Peanut oil was used as the vehicle for a suspension of aluminum penicillin. It was found that when 300,000 units was given intramuscularly to human subjects blood levels of 0.03 unit per cubic centimeter of serum were found to persist from twelve to twenty-four hours. In this study 18 to 22 Gm. mice were given injections of an eighteen hour broth culture of Diplococcus pneumoniae type I (SVi strain) containing 1,000 minimum lethal doses. When the results from aluminum penicillin were compared with those from sodium crystalline penicillin in peanut oil and white wax, and also from calcium penicillin in peanut oil, it was found that the aluminum penicillin was superior in protective ability to any of the compounds tested. Inasmuch as aluminum penicillin is soluble in water, it is suggested that the aluminum salt is converted into a sodium salt before it is absorbed and that this allows for the prolonged action.

Hansen, Galveston, Texas.

Side Reactions to Pyribenzamine Medication. Spencer F. Brown, Proc. Soc. Exper. Biol. & Med. **67**:373 (March) 1948.

All the patients studied were receiving injections of typhoid vaccine, and the effect of tripelennamine (pyribenzamine®) hydrochloride on their reactions was studied. A series of 48 adult patients on 100 occasions was given five 50 mg. tablets of tripelennamine hydrochloride, and 49 subjects on 102 occasions were given placebos. Thirty-seven subjects on 56 occasions were given ten 50 mg. tablets of tripelennamine hydrochloride with double the dose. Each subject on a report sheet recorded whether or not he had any symptoms. Drowsiness was the most commonly reported side reaction to the drug. The incidence was 37 per cent, as compared with 30 per cent in those who received placebos. Nausea, dizziness and insomnia were somewhat more frequent in the patients given the tripelennamine hydrochloride. Headache was less frequent, and nervousness and dryness of the

mouth were apparently equally frequent in both groups. All the side reactions occurred more frequently when the dose of tripelennamine hydrochloride was doubled.

HANSEN, Galveston, Texas.

CENTRAL INHIBITORY EFFECTS OF CARBON DIOXIDE: III. MAN. G. H. POLLOCK, S. N. STEIN and K. GYARFAS, Proc. Soc. Exper. Biol. & Med. **70**:291 (Feb.) 1949.

Eighteen patients with neuroses or psychoses were allowed to inhale various mixtures of carbon dioxide and oxygen and were stimulated electrically for 0.5 second (Offner electroshock apparatus), and the shock was repeated after five minutes without carbon dioxide. Without carbon dioxide, the electrical stimulus resulted in grand mal seizures, but concentrations of carbon dioxide of from 15 to 30 per cent routinely prevented the seizures. With 30 per cent carbon dioxide in oxygen, inhalation of thirty seconds was sufficient. With 15 to 20 per cent mixtures, slightly longer periods of inhalation were required to prevent seizures.

HANSEN, Galveston, Texas.

STREPTOMYCIN THERAPY IN PEDIATRICS. J. CATHALA and R. BASTIN, Presse méd. **56**:118 (Feb. 21) 1948.

This was one of the research studies set up by the French Ministry of Health in 1947. One hundred and nineteen children were included in this series. There were 7 with influenzal meningitis, 5 of whom recovered. The 2 deaths were of infants 3 and 7 months old, respectively; the disease was in the late stages on their entry. Serum and sulfonamides were not used in these 2 infants, and the amounts of streptomycin administered were not as large as those given the patients who recovered.

Ten patients with whooping cough were treated. Two died, but there was definite improvement in the others, including 1 with encephalitis.

One patient with typhoid died while under treatment; another recovered after one relapse. A single patient with salmonella meningitis recovered, and one with colon bacillus meningitis also recovered. Ninety-eight patients in the series had tuberculosis in some form. Forty-one with tuberculous meningitis were treated.

Children under 3 years received daily doses of 400,000 to 600,000 units and children over 3 years of age received 600,000 to 1,000,000 units. At first streptomycin was used intrathecally, but when it was noted that the intrathecal concentration of streptomycin was essentially as high as that with intramuscular injection alone it was decided to use only the intramuscular route. Twenty-four patients died. Twelve are still under treatment. In the 5 in whom no relapse has occurred, 3 have serious sequelae and in 2 the disease seems satisfactorily arrested—two hundred and thirty-two and one hundred and seventy-three days after cessation of treatment. Twenty-one patients with miliary tuberculosis were treated, 8 of whom are dead, 8 of whom are still under treatment and only 2 of whom seem cured. Sixteen patients having tuberculosis with meningitis were treated, with satisfactory results in 4. In the 14 patients with primary infection, the best results were obtained with the outcome in 9 definitely favorable. Three patients with pulmonary tuberculosis with cavitation were treated, but only 1 was cured. Three patients with tuberculosis of bone were also treated, with a favorable outcome in 1.

DAFFINEE, Melrose, Mass.

DISTURBANCES FROM COLD IN SUBTROPICAL CLIMATES. ERICH NASSAU, Ann. pædiat. **171**:167 (Sept.) 1948.

The detrimental effects of cold observed in young infants during the damp and cold season in Palestine are described. The damage consisted of changes in the parts of the skin which were exposed to the cold (swelling, blue and red discoloration), subnormal temperatures and a tendency to pulmonary complications. In severe cases death ensued, caused by pulmonary edema. Recommended therapeutic measures are special care during rewarming of previously exposed parts and administration of cardiac stimulants, lobeline, oxygen and plasma transfusions.

FROM THE AUTHOR'S SUMMARY.

CALOMEL DISEASE IN INFANCY. WILHELM FALK, Helvet. paediat. acta **3**:282 (Sept.) 1948.

A rash, showing the typical picture of calomel disease, appeared in a 9 month old infant following oral doses of calomel (mild mercurous chloride U.S.P.) A grayish brown pigmentation of the skin persisted over a remarkably long period. There were no complications, and the child recovered completely. An attempt to identify specific antibodies was unsuccessful.

FROM THE AUTHOR'S SUMMARY.

GLYCEMIA IN THE COURSE OF STREPTOMYCIN THERAPY. ALVARO MASI and OSVALDO CECCARELLI, Rev. clin. pediat. **46**:192 (March) 1948.

The authors report on the behavior of glycemia in patients with tuberculous diseases and in healthy persons who underwent treatment with streptomycin. From the results obtained, they draw the conclusion that this antibiotic has a slight hyperglycemic action.

FROM THE AUTHORS' SUMMARY.

RHINITIS MEDICINE (NOSE DROPS) AS A CAUSE OF POISONING. ARVO ARVOLA, Ann. med. int. Fenniae **36**:228, 1947.

A female infant 3 years of age was given 8 drops of 1:1,000 solution of 2-naphthyl-1-methylimidazoline hydrochloride intranasally. Two and a half hours later she became unconscious for twenty-four hours and had respiratory failure and bradycardia. The infant was discharged healthy from the hospital two days later. No allergic manifestations were noted in the family. Pharmaceutical products containing the drug are, among others, naphazoline (privine®) hydrochloride, "biogan," "rimidol" and "medicoryn."

WALLGREN, Stockholm, Sweden.

PERORAL ADMINISTRATION OF PENICILLIN TO PREMATURE AND FULL TERM INFANTS. R. GOSTOF and H. TROJANOVÁ, Paediat. danub. **3**:117 (March) 1948.

In premature infants, there is almost no difference in the effects of penicillin given by mouth and intramuscularly. The oral method of administration presents, however, many advantages. The level of penicillin in the blood remains satisfactory for six hours following administration of a single dose of 5,000 units. As, however, the aim is to attain a constant level, it is advisable to give a dose every four hours. According to our experience, the same results can be achieved in full

term newborn babies with doses of 10,000 units. In infants older than 1 month of age the correct way of administering penicillin is in doses of at least 5,000 units intramuscularly every three hours. In older patients it is advisable to give 8,000 units a day for each kilogram of body weight.

FROM THE AUTHORS' SUMMARY.

SYMPATHOGONIOMA. O. TEYSCHL, Pediat. listy **4**:49, 1949.

On the basis of his experience gained from 6 cases (of children aged 1 to 7 years) and the literature, the author discusses the diagnosis, therapy and prognosis of these tumors.

FROM THE AUTHOR'S SUMMARY.

THERAPY OF HYPERPYREXIA IN INFANTS. P. SEVCIK, Pediat. listy **4**:64, 1949.

The majority of infants admitted to the children's department of the hospital in Jihlava, Czechoslovakia, in a serious condition with a temperature of 40.6 to 42 C. (105 to 107.6 F.) died a few minutes after admission, before the usual treatment could produce any effect. The temperature was caused either by a serious basic disease (bronchiolitis, encephalitis, postoperative hyperthermia) or by dehydration and poor care of the infants by their parents, who overdress the children in this district. During the last year the author carried out in 42 infants an immediate intravenous infusion of isotonic dextrose solution, 20 cc. per kilogram of body weight, as a first therapeutic measure, after which the ordinary treatment followed. These infants were usually considered as lost according to previous experience. In this way it was possible to save 33 infants. Infusions of sodium chloride solution are contraindicated, as they increase chloremia.

FROM THE AUTHOR'S SUMMARY.

Book Reviews

In the Name of Humanity! By Joseph Lewis. Price, $2. Pp. 158, with 6 illustrations. New York: The Eugenics Publishing Company, Inc., 1949.

This is a militant book against circumcision as a ritual performance. The author traces the origin of the custom to the primitive belief that the newborn child has been contaminated by contact with the mother's blood and that he must be cleansed by a blood sacrifice represented by circumcision. In the author's opinion, health and hygiene were not associated with circumcision in biblical times and they are used merely as an excuse for its continued practice today. Some of the ancient and unhygienic methods practiced in ritual circumcision are discussed The author pleads that ritual circumcision be abolished and that the operation be limited to those cases in which a medical indication exists.

Children of To-Day and To-Morrow. By Ethel Dukes and Margaret Hay. Price, $2.50. Pp. 249. The Macmillan Company, 60 5th Ave., New York 11, 1949.

"Children of To-Day and To-Morrow" is written by two English psychologists under the sponsorship of The British Social Hygiene Council. This book is a study of psychologic problems in children. The material is drawn largely from wartime England and describes clearly the methods in use in children's psychiatric clinics.

The style is clear and simple and devoid of technical terms. The book is particularly interesting because of the numerous illustrative case histories which are well described. The authors betray no adherence to any particular school of psychologic thought. They place much greater emphasis on hereditary factors, as illustrated by such expressions as "psychological constitution" and "inherent dispositions," than do their American counterparts.

"Children of To-Day and To-Morrow" is recommended as an interesting and informative book, not only for physicians interested in the psychologic problems of children but for parents, teachers and social workers as well.

The Search for the Beloved: A Clinical Investigation of the Trauma of Birth and Pre-Natal Conditioning. By Nándor Fodor. Price, $5. Pp. 400. Hermitage Press, Inc., 8 E. 61st St., New York 21, 1949.

This book is an attempt to trace the effects of the trauma of birth in man. The subject has been elaborately discussed by Rank and others, but Fodor is the first investigator to document his reports with clinical material.

The validity of the author's theory that human behavior is conditioned largely by birth trauma is based on his own interpretations of the dreams of his patients. His observations and speculations are interesting and provocative.

The book is recommended for pediatricians with psychiatric and, especially, psychoanalytic training but might prove confusing and ununderstandable for others.

Directory of Pediatric Societies *

INTERNATIONAL

Sixth International Congress of Pediatrics

President: Prof. Guido Fanconi.
Secretary: Dr. H. Zellweger, Kinderklinik, Zurich.

American Committee:
President: Dr. Henry F. Hemholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quay Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriquez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secçaõ de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

Asociación Pediatrica de Guatemala

President: Dr. Carlos Manuel Monzon, Plazuela Santuario de Guadalupe, Guadalupe.
Secretary: Dr. Maria Isabel Escobar, Casa del Niño no. 1, Guadalupe.

British Paediatric Society

President: Dr. A. G. Maitland-Jones.
Secretary: Dr. Alan Moncrieff, Institute of Child Health, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Bulgarian Pediatric Society

President: Dr. L. Ratchew, University Children's Hospital, Wassil Kolarow 46, Sofia.

Chinese Pediatric Society

President: Dr. Fu-tang Chu, Peking Children's Hospital, Peking, China.
Secretary: Dr. Hua-kang Chow, Peking Union Medical College, Peking, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Czechoslovak Pediatric Society

Chairman: Prof. Dr. Jiri Brdlík, 2 Sokolská, Prague II.

Danish Pediatric Society

Chairman: Prof. Preben Plum.
Secretary: Dr. Elin Fog, Søllingsyey 17, Charlottenlund, Denmark.

German Pediatric Society

President: Dr. H. Kleinschmidt.
Secretary: Dr. F. Goebel, 5 Moorenstrasse, Düsseldorf, Germany (British Zone).

Hellenic Society of Pediatrics

President: Dr. C. Saroglou, Patission St. 74, Athens, Greece.
Secretary-General: Dr. S. Charocopos, Alexandras Ave. 1, Athens, Greece.

Indian Pediatric Society

President: Dr. K. C. Chaudhuri, Dept. of Pediatrics, Medical College, Calcutta.
Secretary: Dr. S. P. Bhattacharjee, Dept. of Pediatrics, Medical College, Calcutta.
Place: Office of the Indian Medical Association, 67 Dharamtala St., Calcutta 13.
Time: Every second and fourth Wednesday of each month.

Medical Association of Israel, National Pediatric Society

President: Prof. L. F. Meyer, 29 Idelson St., Tel-Aviv, Israel.
Secretary: Dr. W. Hirsch, Hadassah Municipal Hospital, Tel-Aviv, Israel.

Nederlandsche Vereeninging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

See Medical Association of Israel, National Pediatric Society.

Pediatric Society of New Zealand

President: Dr. Lawrence Ludbrook, The Lister Building, Victoria Street East, Auckland.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Dr. Kenneth Tollerman.
Secretary: Dr. I. M. Anderson; Dr. Ronald MacKeith.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft für Pädiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela D., Casilla 272, La Paz, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedad Chilena de Pediatria

President: Dr. Miguel Fabres Izaga.
Secretary-General: Dr. Oscar Undurraga A., Merced 565, Santiago, Chile.
Place: Medical Society, Merced 565, Santiago, Chile. Time: 7 p. m., every Thursday.

Sociedad Cubana de Pediatria

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Jaime Jorge, Jose Joaquin Perez, no. 25, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Alberto Peguero, V., Ave. Bolivar 113, P. O. Box 464, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

SOCIEDAD ECUATORIANA DE PEDIATRIA

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Roberto L. Sanchez.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDADE PORTUGUÊSA DE PEDIATRIA

President: Prof. Castro Freire.
Secretary-Generale: Dr. Cordeiro Ferreira, Hospital de D. Estefania, Lisbon, Portugal.

SOCIEDAD URUGUAYA DE PEDIATRIA

President: Dr. Conrado Pelfort.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Lya Imber Coronil.
Secretary: Dr. Guillermo Tovar, P. O. Box 5, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÉTÉ DE PÉDIATRIE DE MONTRÉAL

President: Dr. Paul Letondal, 370 E. Roy St., Montreal, Quebec, Canada.
Secretary-Treasurer: Dr. Edmond Baril, 301 Carré Saint-Louis, App. 1, Montreal, Quebec, Canada.
Time: First and Third Thursday of each month.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of each month.

SOCIETÉ POLONAISE DE PÉDIATRIE

President: Dr. Jan Bogdanowicz, Dzialdowska 1, Warsaw.
Secretary: Dr. Zofia Leimbach, Mieroslawskiego 9 m.6, Warsaw.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg. South Africa.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. Sture Siwe, Lund.
Secretary: Dr. K. A. Melin, Färjestadsvägen 16, Bromma.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Docent H. Magnusson, Sachs' Hospital for Children, Stockholm.
Secretary: Dr. M. d'Avignon, Norrtulls Sjukhus, Stockholm.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm and Pediatric Clinic Upsala. Time: Second Friday of each month (except summer).

VIENNA PEDIATRIC SOCIETY

President: Prof. Dr. A. Solé, Karolinen-Kinderspital, Sobieskigasse 31, Vienna 9.
Secretary: Doz. Dr. Asperger, Universitäts-Kinderklinik, Lazarettgasse 14, Vienna 9.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester 7, New York.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Annual Meeting: Place: Chicago. Time: Oct. 14-19, 1950.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Henry H. Gordon, 4200 E. 9th Ave., Denver 7, Colo.
Secretary-Treasurer: Dr. Robert Ward, Bellevue Hospital, New York 16.
Place: French Lick, Ind. Time: 1950.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Henry E. Gallup.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Time: Four meetings a year.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Gordon O. Matthews, 808 Medical-Dental Bldg., Vancouver, B. C.
Secretary-Treasurer: Dr. S. Gorham Babson, 1220 S. W. Taylor St., Portland, Oregon.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Joseph Lyday, 227 16th St., Denver 2.
Secretary-Treasurer: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of Denver or the Colorado General Hospital. Time: Monthly from October to June.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Chester I. Mead, 1930 Truxton Ave., Bakersfield, Calif.
Secretary: Dr. Clement H. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Carl A. Holmes, 1401 N. 7th Ave., Phoenix.
Secretary-Treasurer: Jacob M. Sobol, 607 Heard Bldg., Phoenix.
Place: Phoenix or Tucson. Time: On Call.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Howard J. Morrison, 444 Drayton St., Savannah.
Secretary-Treasurer: Dr. J. Harry Lange, 490 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SOCIETY

Chairman: Dr. Thurman B. Givan, 115 Remsen St., Brooklyn 2.
Secretary: Dr. Reginald A. Higgons, Port Chester.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Robert J. Mason, 308 N. Woodward Ave., Birmingham, Michigan.
Secretary: Dr. Horace L. French, 301 Seymour Ave., Lansing, Michigan.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

MONTANA PEDIATRIC SOCIETY

President: Dr. Edward A. Hagmann, 208 N. Broadway, Billings, Montana.
Secretary: Dr. George W. Nelson, 2814 9th Ave. N., Billings, Montana.
Place: Decided at each meeting—Spring and Fall.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. George E. Stafford, 823 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Donald C. Nilsson, 115 North 40 Street, Omaha, Neb.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. Edward L. Tuohy, Manchester.
Secretary-Treasurer: Dr. William D. Penhale, Concord.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.
Secretary: Dr. N. T. Crane, 147 E. 7th St., Plainfield, N. J.

NEW MEXICO STATE PEDIATRIC SOCIETY

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Jean Craven, 19 W. Third St., Lexington, N. C.
Secretary-Treasurer: Dr. Susan C. Dees, Duke Hospital, Durham, N. C.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

North Dakota Pediatric Society

President: Dr. R. E. Dyson, Northwest Clinic, Minot, N. D.
Secretary-Treasurer: Dr. William J. Ball, Northwest Clinic, Minot, N. D.
Place: Fargo Clinic, Fargo, N. D. Time: October 15.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

Philippine Pediatric Society

President: Dr. Alberto V. Tupas, Philippine General Hospital, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Philippine General Hospital, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

Texas Pediatric Society

President: Dr. Thomas D. McCrummen, 304 Capitol Nat'l Bank Bldg., Austin, Texas.
Secretary: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Treasurer: Dr. Edith Bonnet, 228 Medical Arts Bldg., San Antonio, Texas.

Virginia Pediatric Society

President: Dr. C. P. Brown, 142 W. York St., Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virignia State Medical Society, Section on Pediatrics

President: Dr. K. J. Winters, 1411 Wauwatosa Ave., Milwaukee 13, Wis.
Secretary: Dr. Niels L. Low, 744 Main St., Racine, Wisconsin.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. Charles H. York, 10465 Carnegie Ave., Cleveland 6.
Secretary: Dr. Earl E. Smith, 10640 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. J. Edmund Bradley, University Hospital, Baltimore 1.
Secretary: Dr. Wilson Grubb, 4 E. 33rd St., Baltimore 18.

Bronx Pediatric Society

President: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Secretary: Dr. George Weiss, 790 Grand Concourse, New York 51.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Secretary: Dr. Stanley S. Lamm, 20 Plaza St., Brooklyn 17.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica, N. Y.
Secretary-Treasurer: Dr. Fred W. Bush, 11 N. Goodman St., Rochester, N. Y.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Central Ohio Pediatric Society

President: Dr. E. H. Baxter, 327 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. E. V. Turner, 2479 E. Main St., Columbus, Ohio.
Place: As Announced. Time: On call.

Chicago Pediatric Society

President Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Secretary: Dr. Alfred S. Traisman, 6349 N. Clark St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

Detroit Pediatric Society

President: Dr. Wilfred D. H. Nolting, 16840 E. Warren, Detroit.
Secretary: Dr. Ruben Meyer, 938 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

Fort Worth Pediatric Society

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Fort Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

Honolulu Pediatric Society

President: Dr. F. D. Nance, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu.
Place: At doctors' homes in rotation. Third Thursday of each month, 6 p. m.

Houston Pediatric Society

President: Dr. Byron P. York, 3911 Montrose Blvd., Houston, Texas.
Secretary: Dr. David Schrum, 3207 Montrose Blvd., Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., fourth Tuesday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Jacob Rosenblum, 161 Rugby Rd., Brooklyn.
Secretary: Dr. Irving Weinstock, 350 Ocean Ave., Brooklyn.
Place: Kings County Medical Society. Time: 8:30 p. m., fourth Monday of October, November, January, March, and April.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2032 Belmont Rd. N. W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: Spring and fall.

Memphis Pediatric Society

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

Milwaukee Pediatric Society

President: Dr. A. L. Kastner, 1810 West Wisconsin Ave., Milwaukee 3, Wis.
Secretary-Treasurer: Dr. A. L. Babbitz, 606 West Wisconsin Ave., Milwaukee 3, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

Nashville Pediatric Society

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Arthur F. Anderson, 122 E. 76th St., N. Y., N. Y.
Secretary: Dr. L. Emmett Holt Jr., 477 First Ave., N. Y., N. Y.
Place: New York Academy of Medicine, 2 E. 103rd St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. T. F. McNair Scott, 1740 Bainbridge St., Philadelphia 46, Pa.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22nd St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. J. A. Gilmartin, 3708-15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

Queens Pediatric Society

President: Dr. Harold T. Vogel, 34-20, 86 St., Jackson Heights, N. Y.
Secretary: Dr. Moe Goldstein, 111-32, 76th Ave., Forest Hills, L. I.
Place: Forest Hills, N. Y. Time: Third Monday of October 1950, February and April 1951, and first Monday of December 1950.

Richmond Pediatric Society

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Merl J. Carson, 500 S. Kingshighway, St. Louis.
Secretary-Treasurer: Dr. Jackson K. Eto, 734 Missouri Theatre Bldg., St. Louis 3.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

San Antonio Pediatric Society

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

Seattle Pediatric Society

President: Dr. David M. Harris, Medical Arts Bldg., Seattle 1.
Secretary: Dr. William A. Jaquette Jr., 1305 Seneca, Seattle 1.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

Waco Pediatric Society

President: Dr. F. William Hoehn, 1422 Austin Ave., Waco, Texas.
Secretary: Dr. J. M. Garrett, 1408 Austin Ave., Waco, Texas.
Place: Providence Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).

Western Michigan Pediatric Society

President: Dr. Horace L. French, 301 Seymour Ave., Lansing, Michigan.
Secretary-Treasurer: Dr. John C. Montgomery, 1810 Wealthy St. S. E., Grand Rapids, Michigan.
Time: Meets on the first Wednesday in October, November, April and May of each year. Two meetings are held in Grand Rapids and two in other designated localities.

Wichita Pediatric Society

President: Dr. Walter L. Schafer, 401 N. Emporia St., Wichita 2, Kan.
Secretary: Dr. William F. McGuire, 401 N. Emporia St., Wichita 2, Kan.
Place: Variable: Time: First Thursday of each month.

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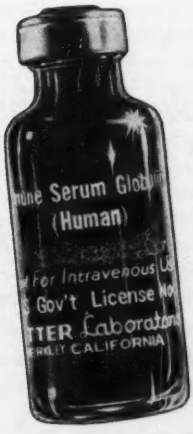

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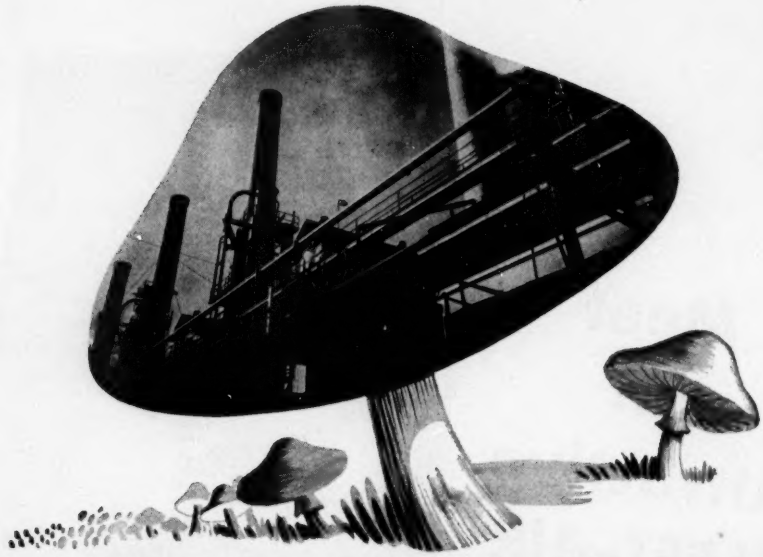

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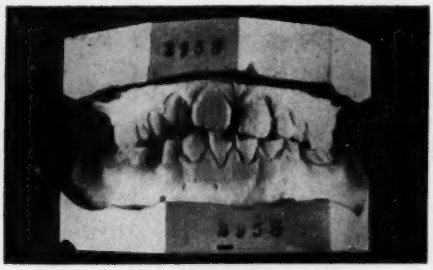

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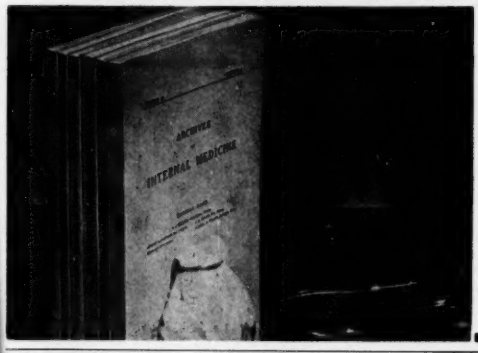

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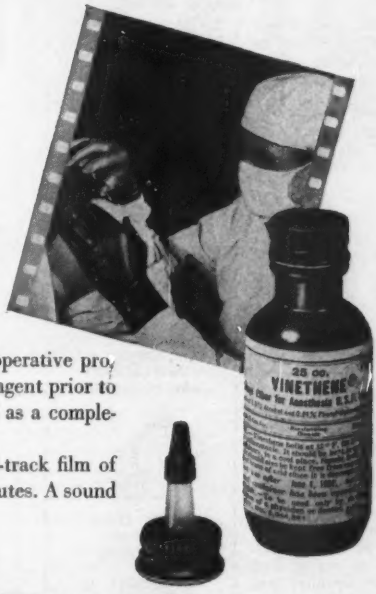

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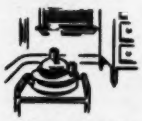

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